RADIOLOGY

A MONTHLY JOURNAL DEVOTED TO CLINICAL RADIOLOGY AND ALLIED SCIENCES
PUBLISHED BY THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

VOL. 28 FEBRUARY, 1937 NO. 2

CANCER OF THE THYROID IN CHILDREN[1]

By HUGH F. HARE, M.D., The Lahey Clinic, *Boston, Mass.*

A SURVEY of 15,000 thyroid operations performed at the Lahey Clinic shows that 258 cases, or 1.7 per cent, were diagnosed as primary malignancy of the thyroid gland. Six of the cases were in children under fourteen years of age, the youngest in this group being six years, the oldest thirteen. Three of the six have been previously reported by Cattell (1). A review and the subsequent course of these cases is given, in addition to the report of three new cases.

There is considerable discrepancy among experienced pathologists regarding the proper classification of thyroid malignancy. We are accustomed to and use Dr. Shields Warren's classification. While it does not reach Dr. Warren's ideal, it is a satisfactory working classification from the clinical point of view. Our classification is as follows:

Group I (1) Fetal adenoma with blood vessel invasion
(2) Papillary adenocystoma with blood vessel invasion

Group II Adenocarcinoma
(1) Papillary
(2) Alveolar

Group III (1) Diffuse small-cell carcinoma
(2) Small compact-cell carcinoma
(3) Giant-cell carcinoma
(4) Fibrosarcoma

[1] Presented before the Radiological Society of North America at the Twenty-second Annual Meeting, at Cincinnati, Nov. 30–Dec. 4, 1936.

It has been noted previously that from 90 to 95 per cent of malignancies of the thyroid develop in pre-existing adenomas, usually in glands in which a single adenoma is present. If early diagnosis and consequently a high percentage of cures are to be attained, this alone is indication for surgical removal of these lesions. Malignancies developing in pre-existing adenoma are largely of the Group I and Group II types. These groups, representing the slower growing tumors and therefore the easiest to cure, make it imperative to arrive at as early a diagnosis as possible.

Tumors making up Group I, namely, the fetal adenomas and the papillary cyst adenomas with blood vessel invasion, grow slowly. Recurrences tend to be local rather than to distant points. Our series of malignancies of the thyroid shows that 95 per cent of these tumors are cured by combined surgery and radiation. This being the group most favorable for treatment, it is unfortunate that none of them occurred in this series.

Tumors making up our Group II, namely, the papillary adenocarcinomas and the alveolar adenocarcinomas, grow more rapidly than those in Group I. They tend to invade surrounding tissues, and recurrences may be local or distant but most frequently spread to surrounding lymph glands, this being the group of thyroid tumors which metastasize to bones. The alveolar adenocarcinomas are more highly malignant than the papillary adenocar-

Fig. 1.

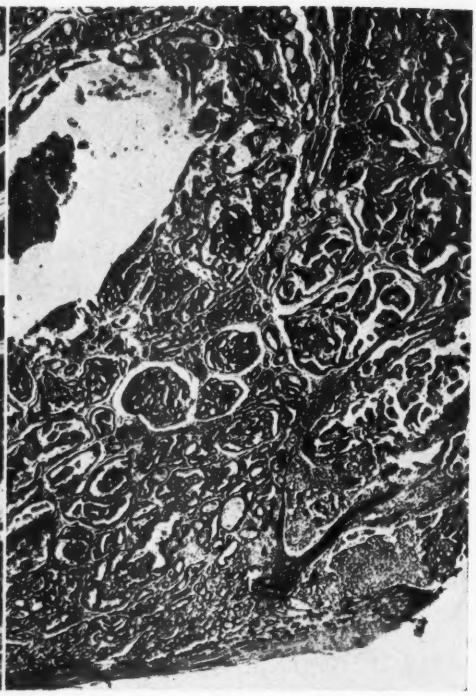

Fig. 2-*A*.

Fig. 1. Case 1. Photomicrograph of tissue from adenocarcinoma arising in and completely encapsulated in a thyroglossal cyst.

Fig. 2-*A*. Case 2. Photomicrograph of tissue from papillary adenocarcinoma (Grade II) arising in aberrant thyroid tissue.

cinoma and, therefore, have proven themselves more resistant to treatment. Four of our six cases fall into Group II.

Group III malignancies, namely, the diffuse small-cell, the small compact-cell, the giant-cell carcinomas, and the fibrosarcomas are the most rapidly growing of thyroid tumors and represent the group most difficult to diagnose pathologically. The pathologic classifications for this group of tumors are varied and confusing. The history of a rapidly growing tumor and the presence of a non-encapsulated diffuse hard tumor must aid in making the diagnosis even when one is accustomed to the various classifications. These tumors are more radiosensitive than the other thyroid tumors but are not as radiosensitive as the lymphoblastomas which the small compact cell tumors closely resemble microscopically. Two of our cases in children have been tumors of this type.

Tumors of thyroid origin may occur in aberrant thyroid tissue, that is, in lateral and medial aberrant thyroid masses and in thyroglossal cysts. These tumors are frequently malignant. Cattell and Albright have recently reviewed 30 cases of aberrant thyroid tumors which have been treated in the Lahey Clinic. Of these, 60 per cent, or 18, were malignant. Further, aberrant thyroid tumors, as one would expect, occur most frequently under forty years of age, 63 per cent of our cases being under this age. Clinically, the differential diagnosis between this type of tumor and other tumors occurring in the neck, such as lymphoblastoma, tuberculous cervical adenitis, dermoid cyst, thyroglossal cyst, branchial cleft cyst, chronic cervical adenitis, and metastatic carcinoma is usually impossible.

Thirty-three per cent, or two of our six cases in children, developed in aberrant thyroid tissue.

One of our cases which fortunately showed a completely encapsulated adenocarcinoma occurred in a thyroglossal cyst.

DIAGNOSIS

With the present methods of clinical diagnosis, the pre-operative diagnosis of malignancy for early cases is practically hopeless. The history of a gland or a pre-existing adenoma increasing in size is suggestive, though not diagnostic. Constitutional symptoms are strikingly absent in the early cases and even in the advanced cases there are few symptoms other than those caused by pressure. Loss of weight is not infrequent. Differentiation from thyroiditis in which the gland increases in size and is firm and hard is many times impossible. It is true that experienced palpators of the thyroid will have higher percentages of correct diagnoses than the untrained but even the best are correct in less than one-third of the cases other than those that are obviously malignant. This means, from the practical point of view, that one must lean entirely upon the pathologist for diagnosis in the early cases. It means that many innocent adenomas must be removed in order to protect the individuals who have or may later develop cancer. In aberrant tissue we know of no way to make the differential diagnosis a certainty other than by biopsy, which we feel should be done in every case.

CASE REPORTS

Case 1. A male child, six years of age, was admitted Feb. 10, 1930, complaining of swelling of four weeks' duration in the midline of the neck, the swelling becoming progressively more marked, yet unaccompanied by constitutional symptoms. The physical examination was negative except for a lime-sized mass in the neck. A clinical diagnosis of thyroglossal cyst was made and operation advised.

On Feb. 12, 1930, a radical resection of the cyst was performed and, while there was no suspicion of malignancy pre-operatively nor at operation, the pathologic diagnosis was adenocarcinoma arising in and completely encapsulated in a thyroglossal cyst. Fourteen days after the first operation, a wider excision was made because of the pathologic report.

In October, 1930, the patient returned for a routine check-up, at which time the cyst had recurred; another excision was advised and performed on Oct. 17, 1930, at which time no evidence of carcinoma clinically or pathologically was found. X-ray treatment was advised, but refused by the child's parents.

A letter from the boy's father three years post-operatively stated that his son was in perfect health and had had no trouble with his neck since operation.

This is a six-year good result treated entirely by surgical means, and is one of the earliest carcinomas we have had. It is to be noted that the tumor at the time was entirely localized within the cyst wall (Fig. 1).

Case 2. An 11-year-old girl entered the Clinic on Jan. 25, 1930, complaining of lumps in the neck of one and one-half year's duration. The lumps had, from time to time, shown some evidence of growth, but previous treatment before entry had decreased the size of the glands before we saw them. There were no constitutional symptoms and, except for the glands, the child was apparently in good health.

Nine months previous to entry, a biopsy had been performed on one of the glands. The pathologic report at this time had been normal lymphoid tissue. Again three months before entry, a second gland was removed. The pathologic report at this time was papillary cyst adenoma arising in aberrant thyroid tissue. X-ray treatment was advised and given at this time. The child received a total of eight treatments in one and a half months. The exact details of the treatment were not recorded. The glands became definitely smaller fol-

Fig. 2-*B*. Case 2.

Fig. 3-*A*. Case 3.

lowing x-ray therapy but did not entirely disappear.

On Jan. 29, 1930, Dr. Frank H. Lahey performed a radical resection of the right side of the neck. The pathologic report at this time was papillary adenocarcinoma, Grade II, arising in aberrant thyroid tissue. There was no evidence in the pathologic slide of either roentgen reaction or destruction of the tumor cells. Postoperatively, two more x-ray treatments were given, but again the factors used were not recorded.

Three years later, during a routine check-up, a small gland was palpated near the medial end of the right clavicle. This remained the same size for another three years without other evidence of recurrence developing. In July, 1936, the gland was removed surgically. The pathologic report at this time was papillary adenocystoma, malignant. Further x-ray treatment was advised, but because of beginning telangiectasia of the skin and the "red-headed" complexion of the patient, small doses were necessarily applied. A series of twelve treatments of 200 r each were given through two portals of 80 sq. cm. each, one on each side of the neck, using the following factors: 200 kv.p., 25 ma., filtered through 0.5 mm. copper and 1 mm. aluminum, the treatments being given daily for a total dose of 1,200 r units to each portal. There was only slight skin reaction following treatment. The patient is now clinically well nearly six years after the first operation (Fig. 2-*B*). While the pathologic report has varied in this case on four different occasions, it merely serves to point out that different types of malignancy may be present in the same case. (See Fig. 2-*A*.)

Case 3. An eight-year-old girl entered the Clinic on Oct. 10, 1935, complaining of a swelling in the neck of one year's duration, the mass having increased in size during the previous three months. The child was in good condition, without symptoms, except that the mother had noticed that she had become nervous along with the increase in size of the mass.

The physical examination was negative except for a dome-shaped, hard, smooth nodule about 2.5×3 cm. in size, slightly to the left of the midline of the neck just above the sternal notch.

The basal metabolic rate was plus and minus 0 on Nov. 11, 1935. Owing to the firmness of the lesion, a pre-operative diagnosis of questionable malignancy was made. On Oct. 11, 1935, Dr. R. B. Cattell excised a lime-sized adenoma of the

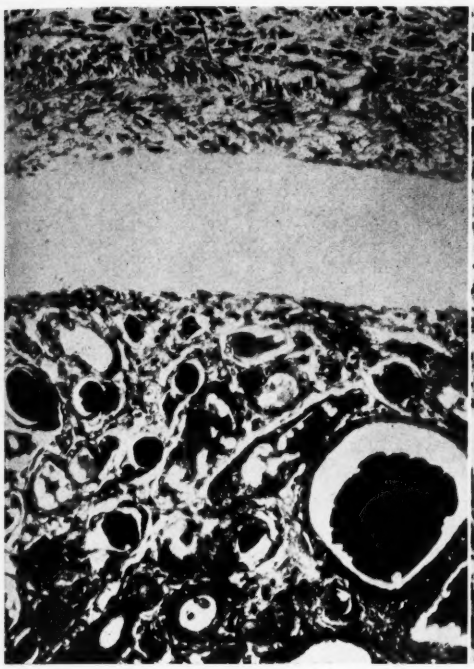

Fig. 3-*B*.

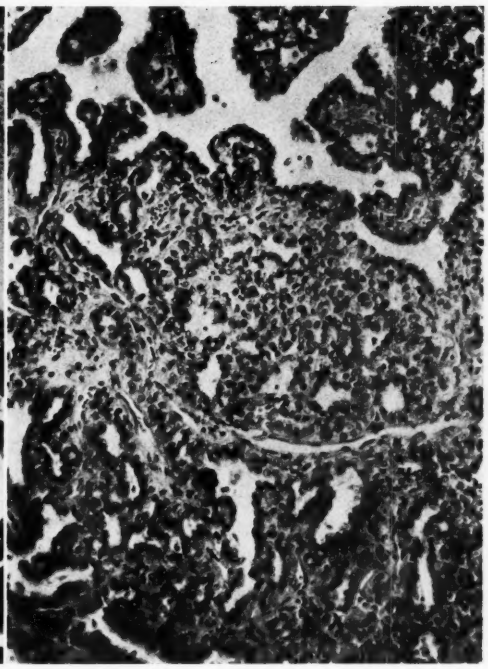

Fig. 4.

Fig. 3-*B*. Case 3. Photomicrograph of tissue from adenocarcinoma arising in the isthmus of the thyroid gland.

Fig. 4. Case 4. Photomicrograph of tissue from papillary adenocarcinoma arising in the thyroid gland.

thyroid which involved the isthmus and which was fixed to the trachea.

The pathologic report was adenocarcinoma with blood vessel invasion. On Oct. 29, 1935, the patient was referred for x-ray therapy. Examination at this time revealed a small gland just above the right clavicle medially which was firm and nonmovable. A diagnosis of recurrence was made at this time and agreed to by the members of the tumor clinic.

A series of 33 x-ray treatments was given through four portals, 80 sq. cm. each, giving 140 r units measured in air, daily, treating through one portal daily, the total dose given to the skin being 4,640 r units. The factors used were as follows: 200 kv.p., 25 ma., 60 cm. distance, filtered through 0.5 mm. copper and 1 mm. aluminum.

The mass which was noted at the start of the x-ray treatment increased in size during the first ten days, then gradually decreased until it was no longer palpable. There was a fairly marked roentgen dermatitis of the anterior portion of the neck accompanying and following the treatment, but about three weeks after the treatments were finished, the skin returned to normal. There were practically no constitutional symptoms noted in using this type of treatment, except that the child complained of sore throat and of some difficulty in swallowing, but this was not marked enough for the child to lose any weight during the course of treatment.

The child remained clinically well following treatment and on March 7, when she returned for a check-up examination four months after the x-ray treatment had been started, a small gland was noted about 3 cm. above the medial end of the left clavicle. It was decided at this time that further x-ray treatment was not in-

dicated as this nodule was close to the skin and it was small enough to be treated easily by radon insertion. Accordingly, 1 mc. of radon, screened through 0.3 mm. gold, was placed in the center of the small gland. The gland gradually decreased in size and two months later was not palpable. The patient has remained well to date without evidence of recurrence, having gained ten pounds in weight and grown nearly three inches in height. This represents a case in which it was necessary to supplement the surgical and x-ray treatment with the use of radon. (See Fig. 3-*B*.)

Case 4. A 13-year-old Jewish girl came to the Clinic in October, 1935, complaining of "goiter" of six months' duration. Her mother had noticed that the thyroid gland had recently increased in size and that it moved up and down noticeably on swallowing. No constitutional symptoms were noted.

The physical examination revealed a well developed and nourished Jewish female, weighing 135 pounds which was her highest weight. The examination was negative except for a hard nodule 4 cm. in diameter to the left of the midline of the isthmus. The basal metabolic rates were plus 6 and plus 4 pre-operatively.

On Nov. 5, 1935, Dr. Richard B. Cattell performed a left subtotal hemithyroidectomy with baring of the trachea, using cyclopropane CO_2 absorption anesthesia. The operative note is as follows: Using a low collar incision, the pre-thyroid muscles were divided transversely between clamps on the left side, and a discrete adenoma of the left lobe and isthmus, which had definitely undergone carcinomatous change, was exposed. It was adherent to the pre-thyroid muscles superficially and extended down slightly below the clavicle. The inferior thyroid artery was ligated as a trunk. The superior pole was not ligated since it was desirable to leave a slight amount of grossly normal gland—approximately the upper fourth was left. The rest of the lobe was totally excised, baring the trachea in the process. The gland had definitely invaded the trachea in a small area. The sternomastoid muscle of this side was not sutured. A section between the proximal and distal cut edges was cut out and the stump ligated, thus leaving a wide exposure for x-ray treatment. A small rubber dam was brought out of the left thyroid bed and the skin closed with clips.

The pathologic report by Dr. Shields Warren was "papillary adenocarcinoma of the thyroid gland."

On Nov. 14, 1935, or nine days postoperatively, the patient was referred for x-ray therapy. The wound was completely healed, but the patient's general condition was excellent, without evidence of recurrence.

A series of twenty x-ray treatments was given through two portals of 80 sq. cm. each, one on each side of the neck, using the following factors: 200 kv.p., 25 ma., 60 cm. distance, filtered through 0.5 mm. copper and 1 mm. aluminum and giving 210 r each treatment for a total dose of 4,200 r units and a dose to each port of 2,100 r, the treatment being given daily.

Three weeks after treatment, the patient returned for observation at which time there was moderate bronzing of the skin of the neck. The wound had completely healed. There were no constitutional symptoms or evidence of recurrence. To date, Nov. 2, 1936, the development of this girl has been normal and there is no evidence of recurrence of her malignancy one year following treatment. (See Fig. 4.)

Case 5. A 13-year-old male came to the Clinic on Oct. 24, 1930, complaining of swelling of the neck of three and one-half months' duration. The swelling had gradually increased in size to the extent that for two months previous to entry dyspnea had been present, especially on exertion. The mother stated that she had noted easy fatigue and irritability, becoming gradually more marked since the start of the swelling of the gland.

The basal metabolic rate was within normal limits, but because of the rapid increase in size of the tumor and because

Fig. 5.

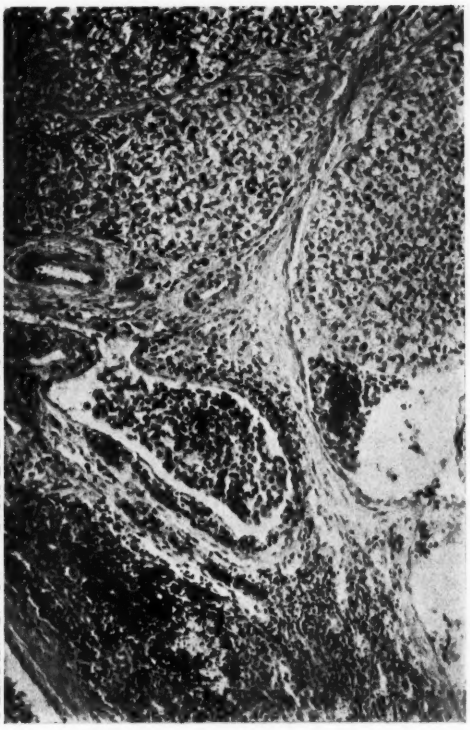

Fig. 6-*A*.

Fig. 5. Case 5. Photomicrograph of tissue from carcinoma of the small-cell type.
Fig. 6-*A*. Case 6. Photomicrograph of tissue from small-cell compact type carcinoma of lateral aberrant thyroid.

of the clinical appearance of the child, a pre-operative diagnosis of malignancy was made. Consequently, on Oct. 27, 1930, Dr. R. B. Cattell performed a tracheotomy, at which time we took a biopsy, as excision was impossible. The pathologic report was carcinoma of the small-cell type, Grade III. The patient was given three series of x-ray treatments between November, 1930, and February, 1931. The factors used were not recorded, but the mass gradually shrank to about one-fourth the size at entry. In the Spring of 1935, the mass began to increase in size again, but further treatment was refused. The patient died at home in December, 1931, fourteen months after his first visit to the Clinic and seventeen months after the first symptoms were noted. This is a case representing a rapidly growing tumor of the thyroid gland, wherein good response was obtained by radiation, but, unfortunately, the necessary amount of treatment to control the lesion even locally was not given, which I feel is definitely a mistake. In many of these cases the disease may be quite advanced without metastatic involvement and every possible attempt should be made to give enough radiation to prevent a recurrence. (See Fig. 5.)

Case 6. A young Jewish girl, nine years of age, entered the Clinic on Nov. 26, 1934, because of an enlargement of the neck of two months' duration, associated with easy fatigability, irritability, nervousness, rapid pulse, and a feeling of more than usual warmth. She had lost two pounds in weight over a period of five months.

The physical examination revealed a poorly nourished young girl, obviously

Fig. 6-*B*. Case 6. Appearance of skin following radiation.

ill and excited. The skin was warm and moist. The pulse rate varied from 112 to 120. The neck revealed firm fixed glands in front of and beneath the sternomastoids, running up under the angle of the jaw on the right. The thyroid gland was enlarged, firm, and fixed. The basal metabolic rate was plus 35.

A pre-operative diagnosis of malignancy or thyroiditis was made. On Nov. 28, 1934, Dr. Frank Lahey excised the glands in the right side of the neck. The pathologic report was as follows: carcinoma simplex, small-cell compact type of lateral aberrant thyroid, with metastases to lymph nodes and with blood vessel invasion.

On Dec. 6, 1934, eight days post-operatively, the wound had healed except for a small area in the lower end of the scar. There were several small palpable glands on the right, indicative of recurrence. A series of sixteen x-ray treatments was given using three 10 × 10 portals, one on each side of the neck and one posteriorly. The following factors were used: 200 kv.p., 25 ma., filtration 0.5 mm. copper, 1 mm. aluminum, distance 50 cm. Three hundred and eight r units measured in air were given at each treatment. Eight treatments were given to the right lateral portal for a dose of 2,464 r units and the other portals received 1,232 r units each. Following the treatment, the patient became dehydrated and acidotic, due to the roentgen sickness and later to radiodermatitis and epithelitis. Hospitalization was essential for three weeks, during which time several transfusions were necessary and the patient was largely fed intravenously and subcutaneously. Her general condition gradually improved along with healing of the neck. On Feb. 2, 1935, a small gland was noted in the right neck about 4 cm. above the right clavicle and behind the sternomastoid muscle. On Feb. 9, 1935, 3 mc. of radon screened through 0.2 mm. of gold were placed in the recurrent node. Following this, there was again considerable reaction of the skin. The nodule decreased in size slowly and gradually disappeared. Her voice became low and somewhat husky for a period of nearly one year, then gradually returned to normal. In October, 1935, another series of treatments was given through two portals, giving 1,500 r each and treating through the left lateral and posterior portions of the neck in order to prevent further treatment over skin previously damaged by the heavy radiation.

Following the treatment, the child began to gain weight and now weighs 77 pounds, a gain of 25 pounds since entry. She is now 54 inches high, a gain of four inches, and there is beginning breast development. Her growth and development have been rapid. Now, two years post-operatively, there is no evidence of recurrence, and the skin of the neck is gradually improving, although there are definite telangiectases present along the right side of the neck. (See Fig. 6-*A*.)

TREATMENT

The treatment of all tumors of the thyroid is primarily surgical—in the early cases for diagnosis and cure; in the advanced cases for diagnosis and, when necessary, tracheotomy. Treatment should never be instituted when the trachea is constricted by the growth to the extent that there is difficulty in breathing, as swelling may occur following treatment which will make an emergency operation necessary.

The use of x-ray treatment for these tumors is a comparatively recent adventure, especially in children. Opinions as to the efficacy of this treatment vary. Group I tumors, that is, the papillary adenocystomas and the fetal adenomas with blood vessel invasion, and the papillary adenocarcinoma which falls under Group II, are agreed upon by all to be radiosensitive. The alveolar adenocarcinomas, the small-cell carcinomas, the giant-cell carcinomas, and the fibrosarcomas are generally considered radioresistant and have been previously so reported by this Clinic (Clute and Warren, in 1934). During the past three years, using a different plan of treatment, we have found that all of these tumors are definitely radiosensitive and that, contrary to opinions previously expressed, they are more so than the Grade I and the papillary adenocarcinomas. The radiosensitivity having been determined, means that x-ray treatment is indicated in all malignancies of the thyroid and it is now our problem to determine the lethal tumor dose of the cancer cell for each individual type. This we are attempting to do now. It will take many cases and several years to do this, but we know now that a larger dose than 1,500 r must be delivered to the tumor cells during one series of treatments and that the probable lethal tumor dose lies close to 3,000 r units.

PLAN OF TREATMENT

In two of our cases (3 and 6), recurrences were noted within two weeks post-operatively, this in spite of careful radical surgery in both cases. It means that x-ray therapy, to be successful, must be given as soon as possible after the diagnosis is made in order to prevent these highly malignant cells from extending beyond the surgical field. There should be no fear of preventing the surgical scar from healing.

In the earlier cases, the treatment given was insufficient and it was largely an artful, rather than a scientific, attempt to destroy the tumor. At first, the treatments were given through a portal large enough to cover the entire neck, and for good measure the superior mediastinum was included. The doses given at each sitting were large—approximately 500 r—and the filtration light—usually 3 mm. of aluminum; at the most, 0.25 mm. of copper and 1 mm. of aluminum. The skin reaction following this type of treatment was severe, causing a severe radiodermatitis and epithelitis over a large area and later giving rise to disfiguring telangiectatic scars which are potentially malignant.

The present method of treatment is to give as large a total dose as possible over a period of from 30 to 45 days, giving a small daily dose of 100 r to each portal, using as factors 200 kv.p., 25 ma., 60 cm. distance, and 80 sq. cm. portal, filtered through 0.5 mm. of copper and 1 mm. of aluminum. Use of this method will allow a higher total dose with less radiodermatitis and epithelitis resulting. We have been able to give up to 2,000 r per portal by this method.

In giving this larger dose, one must be sure that the nutritional needs of the patient are taken care of. The patients are instructed at the beginning to eat a high carbohydrate diet, in order to prevent, as often as possible, roentgen sickness. In about two weeks, the throat usually becomes so sore that a semi-solid high carbohydrate diet is resorted to. The patients are instructed to use a warm aspirin gargle before meals. During the height of the reaction, a liquid diet is advised, but in some cases the reaction is severe enough to require a 1 per cent cocaine alkaloid oil spray for several days in order to be able to force fluids. Loss of weight during and for three to four weeks following treatment is to be expected. Some of our patients have required hospitalization because of the reaction, but no fatalities have thus far resulted from treatment. The skin of children, while more sensitive than the skin of adults, tolerates treatment equally as well. Large doses, as we have outlined, may be given without fear of permanent skin injury.

We have found that malignancies of the thyroid are most likely to recur within

from 12 to 18 months following treatment. This is an indication for frequent follow-up examinations. We prefer to follow our cases every two months.

DISCUSSION

Cancer of thyroid gland origin in children is rare. Few cases are reported in the literature, but, knowing that it does occur, one must remain cognizant of its occasional presence in children and, therefore, must be on the lookout for it always. The occurrence of cancer in aberrant thyroid tissue and its resemblance to tuberculous adenitis and lymphoblastoma make the clinical differentiation impossible. A careful pathologic examination is imperative following biopsy.

These tumors are definitely radiosensitive and, with proper care, excellent palliative results are obtained in all cases. In many cases, cures will be attained if treatment is given before the tumor has spread over too large an area. While we should attempt palliation in every case, I think, too, that we should try to prevent recurrence in the primary field.

Of our six patients, five are living and well; one is dead of the disease. One patient has gone six years without evidence of recurrence; one developed recurrence after three years which was removed surgically and that patient is now without evidence of recurrence. Three cases are without recurrence two years following treatment.

It is interesting to note that of the five living cases, there have been no deleterious effects upon growth. All of these children have thus far developed normally.

None of these children has developed myxedema thus far, in spite of the heavy doses of radiation and in spite of the radical surgery which has been performed. The cholesterol determinations have remained within normal limits and there have been no clinical symptoms to suggest the disease. This has not been true of all of our adult cases, as about 15 per cent of them have developed a mild degree of myxedema following surgery and radiation.

SUMMARY

(1) The primary treatment of all tumors of the thyroid gland is surgical.

(2) Cancers of the thyroid gland are radiosensitive and radiation is indicated in all cases. The lethal tumor dose necessary for destruction of these tumor cells is not known, but an attempt is being made to determine this factor.

(3) Growth has continued normally in all of these children following treatment and none of these cases has developed myxedema following treatment.

(4) Two of our six cases occurred in lateral aberrant thyroid tissue and one case occurred in a thyroglossal cyst.

(5) Six cases of cancer of the thyroid in children under thirteen years of age are reported, of whom five are to-day living and well.

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DISCUSSION

DR. URSUS V. PORTMANN (Cleveland, Ohio): Perhaps one of the reasons why Dr. Hare was kind enough to ask me to dis-

cuss his paper was because he expected me to disagree with him. He has presented a very interesting group of cases under the title "Cancer of the Thyroid in Children." He states that at the Lahey Clinic they have observed about 250 cases which they have diagnosed as malignant disease of the thyroid gland, and of these, six occurred in children. We have observed well over 300 cases that we have reason to believe were malignancies of the thyroid gland and not one was in a child. The youngest patient was a girl of 18 years but no other patient under 20 years has had a true malignancy of the thyroid. Obviously, then, there is a discrepancy and this probably is explainable on the basis of differences in opinion about what should be called malignant thyroid disease. Perhaps I may be able to clarify the matter.

I believe that most or all the cases which Dr. Hare has discussed were reported by Dr. R. B. Cattell in 1932. I have studied them previously and also others which have been reported in the literature, including one by Basil Hughes in 1920, one by Elberts and Fitzgerald in 1927, and a recent one by Ferdinand Lee in 1934. All these cases which have been diagnosed as malignant disease of the thyroid in children have points in common which I would like to mention. There is one exception—this is Dr. Hare's case No. 5. A boy 13 years of age was operated upon for a tumor of the thyroid which was said by the pathologist to be a carcinoma of the thyroid of the small-cell type. He was given irradiation and his condition improved, but then a recurrence developed in nine months, after which he died. Undoubtedly this child had a malignant thyroid—there might be some disagreement about whether it was a carcinoma or a lymphosarcoma. From what I have read about this case and from the histologic appearance of the tissue, I would favor the diagnosis of lymphosarcoma, although I am by no means a pathologist.

Now all of the other cases in this and other reports in the literature about which I know have these points in common:

1. They all are described as having papillary or papilliferous growths or adenocarcinoma originating in papillary cyst adenomas, aberrant thyroid, or the thyroglossal duct. These terms mean pretty much the same thing, namely, that the growths originated in derivatives of the pharyngeal pouch.

2. Distant metastases did not develop in a single instance although many patients had what were looked upon as recurrences.

3. Not one patient died prior to the reporting of the case in the literature and some are still well—for a number of years.

These observations bring up several questions necessitating discussion:

1. Does the histologic appearance of a tumor always satisfactorily or conclusively determine whether it is malignant or benign?

2. If a tissue has histologic appearances similar to those sometimes seen in some thyroid malignancies but the clinical course is benign as far as metastases or the death of some patients is concerned, should the condition be classified as a benign or a malignant disease of the thyroid gland?

3. If a tumor is found to have originated in a derivation of the pharyngeal pouch but not in the thyroid gland *per se*, should the case be classified among the tumors of the thyroid gland?

Let us recall that the thyroglossal duct originates as a tubular structure from the embryonic pharyngeal pouch and extends from the foramen cecum in the tongue down the neck in the midline past the hyoid bone to the location of the normal thyroid gland or even occasionally into the mediastinum. It is lined with epithelial tissue and surrounded by connective tissue, including an abundance of lymphatic structures. Normally this tube closes completely, but not infrequently it fails to close somewhere along its course and fistulæ, cysts, or tumors may develop. When this developmental error occurs, the lining cells of the tube are confined by the surrounding connective tissue to some extent but they continue to multiply, and this results in folds and infolds that have the histologic appearances we call papilliferous structure

in a cyst or a papillary cyst adenoma. Occasionally this confinement of epithelial cells causes them to become very compact masses with little if any recognizable papillary structure—and these are adenomas. Anomalous development of this thyroglossal duct or other derivatives of the pharyngeal pouch may also produce thyroid tissue as aberrant or accessory thyroids at some distance lateral to the midline or in the mediastinum, and this tissue probably may undergo involutional changes like a normally located gland.

The anomalous conditions may become manifest as tumors at any time in life, but especially in childhood, and appear along the course of the thyroglossal tract, lateral to it, outside or inside the thyroid gland or in the mediastinum. Their morphology is essentially papilliferous or adenomatous in character and, therefore, they may have a histologic appearance which may be interpreted as malignancy, but they remain localized and do not destroy vital functions and, in my opinion, are not cancers of the thyroid.

When one of these tumors is excised completely it can never recur. However, the developmental error that caused one of them may also have produced others which may appear later in the same neighborhood or at a distance—even on the opposite side of the neck. These are not recurrences but are new tumors developing coincidentally and if they also are removed they will not recur.

A proof of the non-malignant nature of these tumors is the fact that none of the cases reported in the literature as cancers of the thyroid in childhood, that I know about, have ever developed metastases except the case of the boy previously mentioned. This is not characteristic of malignant disease. Metastases do not develop in spite of the fact that in rare instances the papillary structure apparently has been observed in blood vessels.

Some of these children who were thought to have had malignant tumors have received irradiation and the masses in the neck apparently have been reduced in size or have disappeared; however, I believe that in almost every case the tumor eventually reappeared and subsequently was removed successfully. It is logical to expect that these epithelial tumors would be as highly radioresistant as are normal thyroid tissue and papillary cyst adenomas in other locations. The temporary improvement that appears to follow irradiation probably is due to reduction in the size of the enlarged lymph nodes, which is nearly always associated with these conditions, and not to any great degree of direct destruction of the cells of the tumor. This is probably the explanation, because, after the treatment, the tumors reappear and are excised successfully, as happened in some of Dr. Hare's cases.

I believe that our differences of opinion about what we consider to be malignant diseases of the thyroid have been explained and the original questions answered as follows:

1. The histologic appearance of a tissue is not always satisfactory or conclusive evidence of malignancy, especially when applied to the derivatives of the pharyngeal pouch, including the thyroid gland.

2. Some tumors that originate from pharyngeal pouch derivatives may have some histologic appearances of malignancy but should not be classified as malignant tumors of the thyroid gland, because their clinical course is benign as far as vital functions are concerned.

In my opinion, the cases reported as malignant disease of the thyroid gland were not true malignancies with the exception of one case. I wish to thank Dr. Hare for this opportunity to disagree with him.

DR. HARE (closing): I did not plan to enter into a discussion as to whether or not these were malignant tumors, since I have left the pathologic study and the decision as to malignancy up to the pathologist, Dr. Shields Warren, who has handled more of these tumors than I have.

I have recently gone over our entire series of thyroid cancers with Dr. Warren and he feels very definitely that this group

of cases which have been reported here are malignant. He feels, further, that the Group III cases did not arise in aberrant thyroid tissue; that they arose in the thyroid gland.

One of the other cases which recurred shortly after operation was not an aberrant thyroid tumor.

Of the other cases which occurred in thyroid tissue aberrant, both were in lateral aberrant tissue; and we have had no cases occur in the medial type of aberrant tissue.

As to the diagnosis of lymphosarcoma on my case No. 5, I can only say that the patient did not have the clinical signs that usually accompany a lymphosarcoma or lymphoblastoma, nor have I seen them occur in any of our Group III cases in which the pathologic diagnosis has been small, compact-cell carcinoma. I am quite unwilling to agree to a diagnosis of lymphosarcoma unless the patient will eventually show clinical signs and symptoms compatible with that disease.

So for the time being, I think that we will have to stand by our pathologic classification as it is—the best working classification that we have to date.

X-RAY DIFFRACTION STUDIES OF GLOBULAR PROTEINS

II. HEMOGLOBINS

By GEORGE L. CLARK *and* JOHN H. SHENK, *Urbana, Illinois*
Chemistry Department, University of Illinois

HISTORICAL

IN a comprehensive treatise on the crystallography of hemoglobins, which also includes a complete survey of the literature representing the history of hemoglobin crystallization up to that time, Reichert and Brown (1) gave Hunsfeld (2) the credit for the discovery, in 1840, that hemoglobin crystallizes. He found crystals in blood of the earthworm and also refers to crystals from the blood of man and of the pig. Although Hunsfeld's article is the first on record, K. E. Reichert (3), in 1849, gave us the real beginning of our knowledge of hemoglobin when he discovered tetrahedral crystals of hemoglobin in the fetal membranes and the mucous membrane of a guinea-pig which was examined six hours after death. This discovery stimulated workers to study hemoglobin and a number of articles appeared during the next few years. For some time, all of the crystals that were obtained were gotten solely by accident. Funke (4) is said to be the first to have devised a method for preparing blood crystals. His method, which is very satisfactory for the hemoglobins that crystallize readily, consists of the addition of water to blood on a microscopic slide and observation of the edges of the preparation. Some of the corpuscles vanish while others acquire dark, thick outlines, become angular, and develop into small, sharply defined rods. Funke made measurements of the angles of the crystals by the aid of a goniometer and assigned the crystals to certain systems even though his data were insufficient. He noted that the forms and solubilities of the crystals of different species are not alike and suggested, therefore, that species may thus be differentiated, the proof of which was fully substantiated by the outstanding work of Reichert and Brown. In an article coincident with that of Funke, Kunde (5) also stated that the hemoglobin crystals of different species are different and characteristic of the species. Crystals from various kinds of blood which appear to possess a similar form still showed unmistakable differences in the size of the angles.

Since this early work on the crystallization of hemoglobin, many methods have been proposed for the preparation of more or less pure oxy-hemoglobin in relatively large amounts, beginning as early as 1867 by Hoppe-Seyler (6). The method used was essentially as follows: red corpuscles were laked with water, ether, or a mixture of ether and alcohol and from the solution so obtained, oxy-hemoglobin was separated by crystallization in the cold from approximately 25 per cent alcohol. It was not until the present century that methods were devised for the preparation of a purer product. Barcroft and Roberts (7) washed red corpuscles obtained by centrifuging defibrinated blood with Ringer's solution, laked with ether, filtered through a suitable filter, and dialyzed the solution against ice water. Other processes involving the passage of gases through the hemoglobin solution, freezing and thawing, etc., were used, but the most satisfactory methods to be found for the crystallization of hemoglobin are by the addition of alcohol to, or the adjustment of the p_H of a solution prepared by the method of Marshall and Welker (8), to be described later.

The study of hemoglobin is very difficult because, as has been known for some time, it is quite unstable, whether in crystalline form or in solution, especially in concentrated solution, and undergoes rapid alteration, changing into methemoglobin. Alcohol deleteriously affects the hemo-

globin molecule. Even in dilute solution it lessens its solubility, alters the extinction coefficient, gradually decolorizes the crystals, and may affect the water of crystallization. When dried in air, hemoglobin crystals rapidly lose their crystalline structure—which was noted by Halliburton (9). He also found that repeated crystallization of the hemoglobin of the squirrel changes the crystals from hexagonal plates to rhombic prisms or a mixture of these with rhombic tetrahedra.

The first notable work on the crystallography of hemoglobins was done by Preyer (10). In a survey of the literature, he comes to the conclusion that hemoglobin crystallizes only in the rhombic and hexagonal system because, of the various hemoglobins studied, these two systems are the only ones definitely proven to exist. However, Reichert and Brown (1), after an exhaustive crystallographic study, say that the hemoglobins may crystallize in any system. In their study, it was found that the crystals of the species of any genus belong to the same crystallographic system and generally to the same crystallographic group; and they have approximately the same axial ratios, or their ratios are in simple ratio with each other. In other words, the hemoglobin crystals of any genus are isomorphous.

Hemoglobin is a complex conjugated chromo-protein molecule consisting of a colorless protein radical called "globin," attached to four molecules of a red-brown crystalline non-protein radical called "heme," which gives the color to the molecule. Beside the elements usually found in proteins, hemoglobin also contains phosphorous and iron, being one of the few proteins to contain a metal. Early workers reported a molecular weight of 15,000–17,000 from calculations based upon sulphur content, iron content, combining power for oxygen and carbon monoxide, etc. This value is much too low, as is shown by recent determinations by Wu and Yong (11) from osmotic pressure data, and by Svedberg by means of the ultracentrifugal method. Both reported a molecular weight of 68,000, which is about four times that first reported considering one iron atom per molecule.

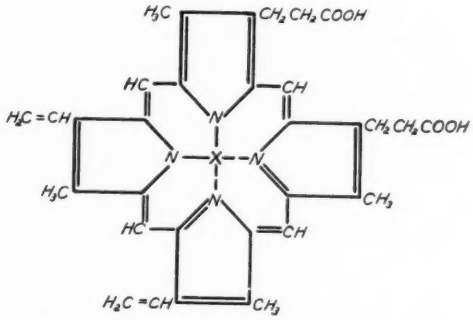

Fig. 1. Formula for hemin. In heme, X = Fe^{++}; in hemin, X = $FeCl^{++}$.

It has long been known that the hemoglobins of different species are different. The most marked differences noted have been in crystalline structure, degree of solubility, and in the quantity of water of crystallization. The crystal structures are so different that the species can be identified. Crystals from ox and hog blood are soluble in their water of crystallization at room temperature, while rat hemoglobin is practically insoluble in cold water. Cohn (12, 13) and his coworkers have shown that they differ also in the ratio of amino acids, the amount of iron and sulphur, as well as in their solubility in salt solutions.

It was suggested very early that the pigment radical in all hemoglobins is the same and that the differences were due to the globin fraction. All later work indicated that this assumption is true. The same heme has been reported by Anson and Mirsky (14) to be present in the animal kingdom in a variety of pigments.

Hemoglobin can exist in solution, as such, only near the neutral point. Dilute acids and alkalies change it into hemochromogen. This change, according to Anson and Mirsky (15), is not a separation of the two fractions as it is ordinarily interpreted, because hemochromogen itself is a conjugated protein. There are many hemochromogens, each one consisting of

an iron-pyrrole molecule (heme) combined with a nitrogen compound. They show that hemochromogen is not simply reduced heme, because it can be prepared from reduced heme by adding a protein to it. They prepared hemochromogens from other proteins, amino acids, amines, ammonia, pyridine, nicotine, pyrole, and other nitrogenous bases and found that they had similar, although not identical, properties. The manner of combination of the two fractions of hemoglobin is not yet known. From the above, it would seem that the combination is probably between a nitrogen group of the globin and the acid groups of heme or a co-ordination binding. The nitrogen group of globin responsible for combination with heme is not necessarily amino nitrogen, because pyridine, which has no amine nitrogen, readily combines with heme, so the combination may be with tryptophane, histidine, or proline. The combination of globin with heme produces a much more soluble substance. In his work on the oxygen equivalent of hemoglobin, Pauling (16) concludes that the four hemes of the molecule are arranged at the corners of a square, each heme being connected with two others.

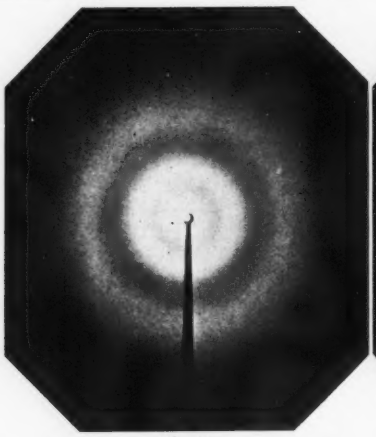

Fig. 2.

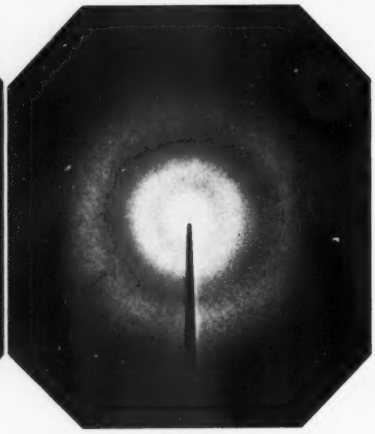

Fig. 3.

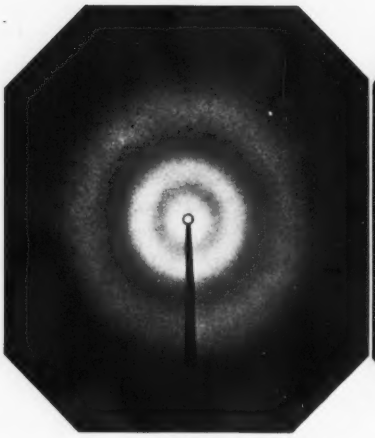

Fig. 4.

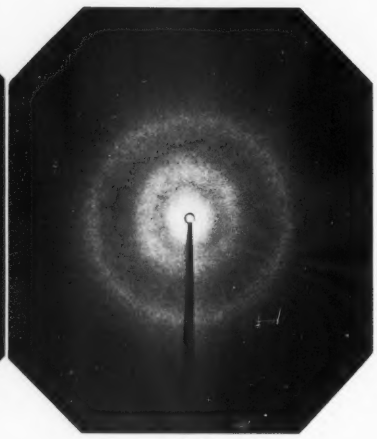

Fig. 5.

Fig. 2. Diffraction pattern of air dried hemoglobin.
Fig. 3. Salt precipitated hemoglobin.
Fig. 4. Picric acid precipitated hemoglobin.
Fig. 5. Trichloroacetic acid precipitated.

In 1901, Nencki and Zaleski (17) reduced chlorophyll and hemoglobin to mixtures of volatile bases called "pyroles," a copper or iron anticathode, no traces of crystalline diffraction effects could be obtained with freshly prepared hemoglobin.

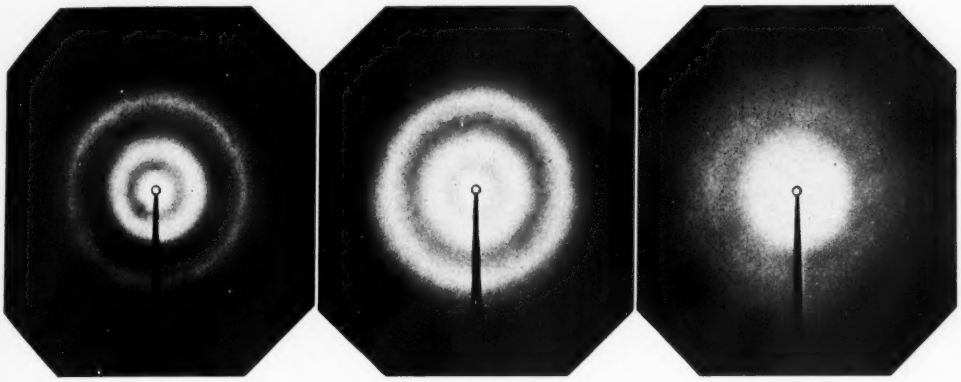

Fig. 6. Fig. 7. Fig. 8.

Fig. 6. Diffraction pattern of heat denatured hemoglobin.
Fig. 7. Alcohol precipitated hemoglobin.
Fig. 8. Hemoglobin, tungstic acid precipitated.

thus showing for the first time that pyrole nuclei were involved in the structure of both pigments. Kuster (18), in 1910, proposed the formula given in Figure 1 for hemin which was completely justified twenty years later by Fischer (19) and his co-workers, who established the correct structure of natural hemin and heme for which Fischer received the Nobel prize in 1930. The pigment is one of the porphyrins. Although the substance represented contains 34 carbon atoms, Herzog (20) reported that it can be converted into a 33 carbon compound, which he believes is the prosthetic group of hemoglobin.

The porphyrin ring, according to (21), is both strainless and flat. On drastic reduction of hemin and heme, Dietz (22) reports that the metal drops out and the porphin ring breaks on either side of the bridge carbon atoms, forming various substituted pyroles. Oxidation removes the bridge carbon atoms completely.

The x-ray analysis of hemoglobin and its hemin derivative has been very limited. Only three papers have appeared, one of which deals only with the gradual disappearance of the two halos as water was taken up. George (23) stated that, using the powder method with soft x-rays from However, Wyckoff and Corey (28) were able to obtain a crystalline pattern by keeping the sample moist during exposure. They reported interplanar spacings and relative intensities for rat hemoglobin.

Denaturation Studies.—Hemoglobin solutions free from other proteins were prepared by the method of Marshall and Welker (8), from which the hemoglobin could be crystallized. The protein in this solution was denatured by various substances, as in the case of egg albumin already described in the first paper of this series, by adding the precipitant until precipitation appeared complete. The various reagents used were the same and the samples were prepared in the same manner as with egg albumin. The x-ray beam from a copper targeted Philips Metalix Diffraction tube was filtered through nickel foil and passed through a 0.025 inch pin hole before transmission through the sample. A flat film 5 cm. from the sample was used for registering the diffraction pattern.

In general, the patterns obtained with hemoglobin are the same as those of the correspondingly treated egg albumin samples, except that the rings are not as sharp. This is probably due to the presence of the pigment fraction of the mole-

cule, although it does not affect the diffraction patterns in any other way. The heme is still present in the combined state because the precipitate is red, which is not the color of free hemin, and it cannot be extracted with alcohol.

Figure 2 shows that dried hemoglobin gives the same two rings—the outer one is quite broad and diffuse. Hemoglobin precipitated by salt solutions (Fig. 3), and the picric acid product, (Fig. 4) gave the same type of diffraction as dry hemoglobin. Again it is noted that the action of trichloroacetic acid on a protein is different from that of picric acid, because relatively sharp rings are obtained. Denaturation of hemoglobin by heat and alcohol gave much sharper patterns than air-dried hemoglobin but not as sharp as the egg albumin patterns; neither do they show the 3.5 Å.U. interference.

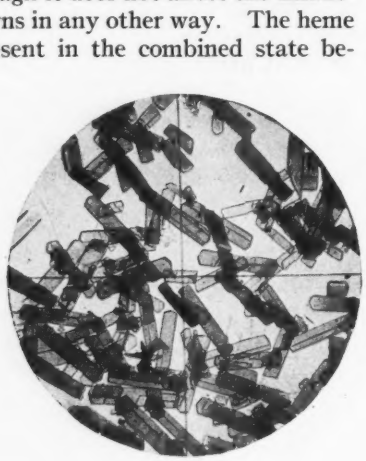

Fig. 9.

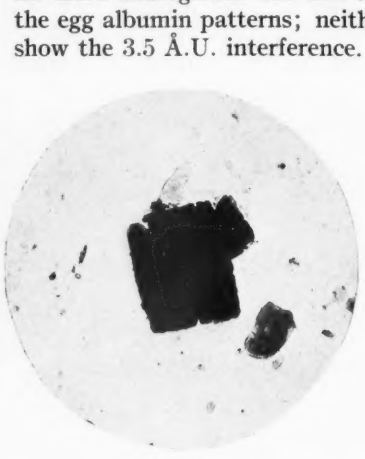

Fig. 10.

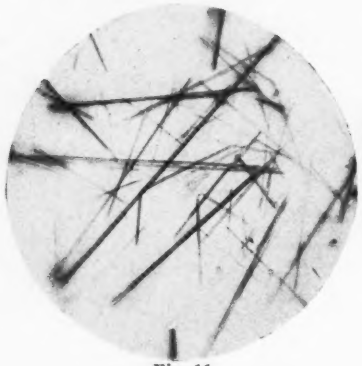

Fig. 11.

Fig. 12.

Fig. 9. Photomicrograph of rat oxyhemoglobin.
Fig. 10. Hog carbon monoxide hemoglobin.
Fig. 11. Horse oxyhemoglobin.
Fig. 12. Horse carbon monoxide hemoglobin.

The tungstic acid precipitate was very highly absorbent but the protein rings appear—if exposed long enough—with rather intense fogging near the central spot.

Crystalline Hemoglobin.—The hemoglobin solution was prepared from blood that had been defibrinated by shaking with glass beads and straining through a cloth. The red corpuscles were separated by centrifuging, washed three or four times with 2 per cent sodium acetate solution, and laked with a minimal quantity of distilled water. When the cells are well laked, the solution is very much

darker. This solution was treated with a sufficient quantity of aluminum hydroxide cream to remove other proteins. Usually about four volumes are added. It was shown by Marshall and Welker (8), in 1913, that aluminum hydroxide cream removes all of the blood proteins except hemoglobin. The aluminum hydroxide cream was prepared by adding 1 per cent ammonium hydroxide slowly, with constant stirring, to a 1 per cent solution of ammonium alum until reaction was just alkaline to litmus. The precipitate was allowed to settle and was washed by decantation until the supernatant liquid gave a negative test for ammonia with Nessler's reagent. To avoid diluting the hemoglobin solution the cream may be centrifuged and the excess of water poured off. Shaking the solution with the cream seems to give a more complete removal of other proteins and a more rapid filtration. A pure solution of oxy-hemoglobin filters rapidly. This is a mild treatment and, therefore, denaturation should be very slight. Oxygen was bubbled slowly through this solution in an ice bath for one hour to insure complete oxygenation. Absolute alcohol was then added slowly with vigorous stirring and the resulting solution placed in the refrigerator for crystallization, which usually took place over night. The amount of alcohol required varies greatly with hemoglobins from different animals, from about 5 per cent for rat hemoglobin to 40 per cent for ox, hog, and sheep hemoglobin. The conditions most favorable for crystallization are a concentrated solution and a low temperature. Hemoglobin prepared in this way is only slightly soluble in

Fig. 13.

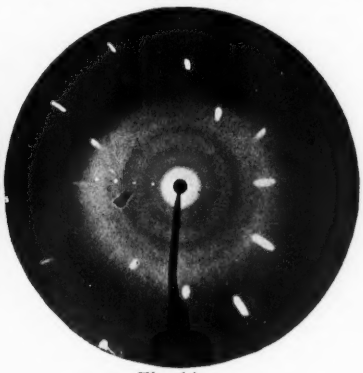

Fig. 14.

Fig. 15.

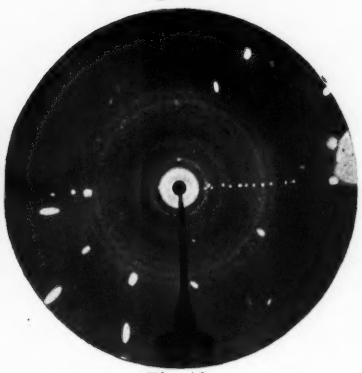

Fig. 16.

Fig. 13. Diffraction pattern of rat oxyhemoglobin.
Fig. 14. Hog carbon monoxide hemoglobin.
Fig. 15. Horse oxyhemoglobin.
Fig. 16. Horse carbon monoxide hemoglobin.

water but may be recrystallized by dissolving the crystal paste by the addition of *N* KOH, drop by drop, with vigorous stirring to avoid denaturation and, after the removal of any insoluble material, the addition of any equivalent amount of 0.1 *N* HCl.

Carbon monoxide hemoglobin is prepared from the above solution by substituting carbon monoxide for oxygen. The solution was carbonylated by saturating with carbon monoxide for one hour, generated by the addition of formic acid to warm concentrated sulphuric acid. The gas was washed twice with a NaOH solution and then with water before it bubbled through the cold hemoglobin solution. Absolute alcohol was added as above and then placed in the refrigerator. Carbonmonoxide hemoglobin is much more stable than the corresponding oxy-hemoglobin. The crystals, from which the mother liquor has been removed, maintain their structure for weeks if kept under an atmosphere of carbon monoxide.

The following crystalline products were obtained: rat oxy-hemoglobin, horse oxyhemoglobin and carbon monoxide hemoglobin, and hog carbon monoxide hemoglobin. The rat and horse hemoglobins were easily crystallized, but the carbon monoxide hemoglobin of hog blood crystallized only after standing in the refrigerator for three weeks. Photomicrographs of the hemoglobin crystals obtained are shown in Figures 9 to 12, and it can readily be seen that there is a distinct difference between hemoglobins of different species.

Rat hemoglobin is probably the easiest to obtain in crystalline form; in fact, a great deal of care must be taken or it will crystallize when the centrifuged cells are laked with water. The crystals belong to the orthorhombic system, but crystallize in thin tabular elongated hexagonal plates. Although some of the crystals are nearly perfect hexagons, most of them have two sides longer than the other four. They show sharp extinction parallel to their long axis when examined in polarized light. The crystals obtained from horse blood are in the form of orthorhombic prisms, usually many times as long as they are wide. If only a small amount of alcohol is used, so that crystallization takes place slower, the ratio of length to width is increased greatly. Practically no difference is observed in the two hemoglobin preparations from horse blood except that the carbon monoxide crystals are not so long, which fact may be due to the higher percentage of alcohol present during crystallization. Both preparations showed sharp extinction of polarized light parallel to the long axis of the crystals. These crystals were very fragile and were crushed unless extreme care was used in placing the cover glass to protect the sample when observations were being made with the microscope. Even stirring of the crystals suspended in their mother liquor would break them.

It was very difficult to obtain crystals from hog blood because of its high solubility. No crystals were obtained from the oxy-hemoglobin preparation and the carbon monoxide hemoglobin crystallized only after standing in the refrigerator for three weeks. Even then, the crystals were not very well formed. They appeared to be orthorhombic, showing cleavage at right-angles and definitely rectangular etch figures. When examined in polarized light, they showed very sharp parallel extinction.

The diffraction patterns of hemoglobin were obtained by placing the crystals on a porous plate until the mother liquor had drained away and then pressing them into a small hole in a brass strip. The crystals were protected during exposure by thin mica sheets. When the patterns were taken in air, at a distance of 5 cm., it was quite fogged and the rings were too close to the central spot to be accurately measured, so the sample and film were placed in a vacuum camera at a specimen to film distance of 10 centimeters. This greatly improves the quality of the photograph and the accuracy of the measurements.

The diffraction patterns, as well as the photomicrographs, show a distinct difference in hemoglobins from different species. (See Figs. 13–16.) The inter-

planar spacings represented by the various rings, together with their relative intensities, are shown in Table I.

The intensities are evaluated thus: v = very, w = weak, s = strong, m = moderately, b = broad, and if there is no designation, the line is of average intensity. All intensities are evaluated relative to the rings on that pattern and are not relative to all the patterns shown. Many of the rings, although easily seen and measured on the film, do not show in the prints but their positions are indicated by ink spots in a straight line across the pattern. The larger spots are produced by the mica windows used to prevent loss of moisture from the sample. Since mica does not give rings, there is no confusion involved by the two patterns being on the same film, as might have been the case if glass had been used.

TABLE I.—INTERPLANAR SPACINGS OF HEMOGLOBINS

Rat Oxy Hb	Horse Oxy Hb	Horse CO Hb	Hog CO Hb
46.4 vs	48.2 vs	48.2 vs	48.2 vs
25.6 b	30.8 s	30.3 s	28.5
21.4 w	24.5 w	24.5 w	17.5
17.2	18.9 b	18.4 b	15.1
15.1	13.3 vw	16.4 vw	9.9 vb
12.7 ms	12.3 vw	13.2 vw	
11.6 vw	11.0	12.1 w	
10.2 ms+b	9.9	10.9	
9.2 w	9.0 w	9.9 ms.	
8.1 w		9.0	
7.5 vw		7.9 vw	
5.81 vw		7.4 vw	
5.2 vw			
4.8 vw			

An examination of Table I shows decided differences between the various patterns, except the carbon monoxide and oxy-hemoglobins of horse blood. The carbon monoxide pattern is a little more intense and, therefore, a few more of the very weak lines can be seen. However, all of the patterns show a long spacing of about 48.2 Å.U., which is probably the long dimension of the unit cell of crystalline hemoglobin. The slight difference between the long spacing of rat oxyhemoglobin and the others is easily within experimental error, and, therefore, does not mean that this difference is characteristic. Although it is reported that crystalline hemoglobin is unstable, crystals examined under the microscope after a thirty-hour exposure to x-rays at room temperature still appeared definitely crystalline and also showed sharp extinction. The carbon monoxide hemoglobin of horse blood was allowed to stand at room temperature for two weeks and it still gave a pattern identical with the one taken when first prepared. It seems that the crystals are fairly stable at room temperature if the excess mother liquor is removed. Although x-rays change hemoglobin in solution to methemoglobin, there was no noticeable change in the crystals treated as above.

Rat hemoglobin crystals prepared by the addition of alcohol and by adjusting the p_H gave identical x-ray patterns. No beta lines could be detected in the patterns, even though a nickel filter was not used.

DERIVATIVES OF THE PIGMENT FRACTION

(*a*) *Hemin.*—Hemoglobin consists of a simple protein called globin combined with the iron pyrrole complex known as heme. The addition of acids under suitable conditions causes a separation of globin and heme, which, during the process of isolation, changes over to its familiar oxidation product, hemin. Hemin differs from heme in that the iron atom has been oxidized to a valence of three and now holds a chlorine atom.

A formic acid hemin was prepared according to the method used by Bruckner (24). Either blood or a hemoglobin solution after the addition of 1 g. of sodium sulphate per liter, was coagulated by heat. The liquid was pressed out of the coagulum and after washing several times with alcohol it was extracted with a 3–4 per cent solution of formic acid in alcohol. The extract was filtered and left at room temperature to crystallize. Although crystals soon began to form, crystallization was not complete for several days. At first, the extract was colored deep red, but upon

standing, it finally became a light tan color and quite transparent.

While this procedure worked quite well, it was found that better results could be obtained by coagulating the protein with alcohol and allowing it to stand over night before filtering. The filtrate from this coagulum is clear and colorless and the crystals are mixed with much less of the amorphous looking material which is always present when coagulated by heat.

The crystals form on the sides and bottom of the beaker and adhere tightly to the glass so that is is difficult to obtain good specimens for photomicrographs. The yield of this hemin is about 1.3 gm. per liter of blood. It is insoluble in methyl and ethyl alcohols, chloroform, ether, acetone, etc., but is soluble in alkali dissolved in water or alcohol, pyridine, and a mixture of chloroform and pyridine. Hemin may be recrystallized from the latter mixture by dissolving 1 g. in 5 ml., filtering, and pouring slowly into 100 ml. of a 10 per cent formic acid solution in alcohol.

According to Bruckner, the substance has an empirical composition corresponding to the following formula: $C_{35}H_{33}O_6H_4.2(C_2H_5OH)$ and represents a formic acid hemin. The substance yields chlorohemin when heated with acetic acid and sodium chloride. The crystals are very dark in color and transmit very little light, but when examined using polarized light they

Fig. 17.

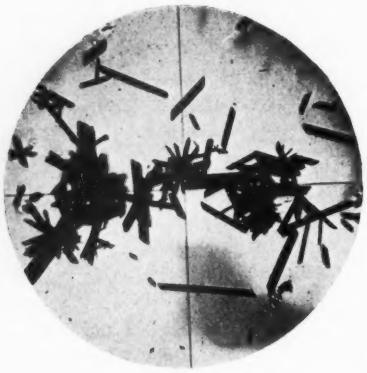

Fig. 18.

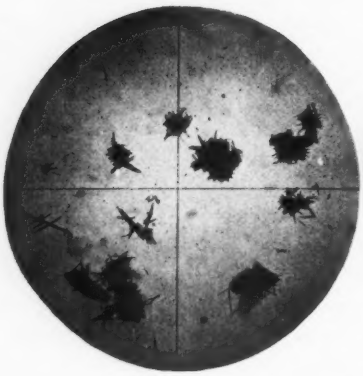

Fig. 19.

Fig. 20.

Fig. 17. Photomicrograph of formic acid extracted hemin.
Fig. 18. Chlorohemin.
Fig. 19. Potassium chlorohemin.
Fig. 20. Potassium oxyhemin.

show definite oblique extinction. A photomicrograph of the crystals obtained is shown in Figure 17 and the x-ray diffraction pattern is shown in Figure 21. The spacing in Å.U. of the hemins prepared with formic and acetic acids together with their relative intensities are given in Table II, with those of chlorohemin and potassium oxyhemin.

TABLE II

Formic Acid Hemin	Acetic Acid Hemin	Chloro-hemin	Potassium Oxyhemin
12.7 vs	11.40 vs	12.50	32.1 ms
10.2 vs	9.73 w	9.86	14.9 vw
8.4 vw	7.98	8.78 s	10.2 s
6.83 vw	6.94	7.60	6.95 s
5.48 vw	5.58 vb	6.54 w+b	6.15 vw
5.11	4.94 w	5.34 s	5.73
4.27	4.48 w	4.71 w+b	5.00 vw
3.84 w	4.06 ms	4.11 b	3.92 vw
3.58 vw	3.63 ms	3.59 vs	3.51 ms
3.34 s	3.24 w+b	3.39 vw+b	
3.00 b	2.95 w+b	3.15 vw+b	
		2.99 vw+b	
		2.78 vw+b	
		2.57 vw+b	

Diffraction patterns and photomicrographs were prepared of hemins from blood of the following animals: rat, horse, hog, and cow. They all give identical diffraction patterns but the photomicrograph varied a little, as is to be expected.

Either methyl alcohol or ethyl alcohol could be used without affecting the diffraction pattern either in line position or relative intensity. An attempt was made to substitute acetic acid for formic acid but without success, even when the acetic acid concentration was considerably increased. In one case, glacial acetic acid was added to hemoglobin which had been coagulated with alcohol, mixed quickly, and then extracted with methyl alcohol. The filtered extract was much darker than that obtained with 4–20 per cent acetic acid and upon standing, a thin crystalline deposit was formed, which gave the diffraction pattern, Figure 22. It is readily noted that the pattern is quite different from that obtained by formic acid extraction. The nature of the splitting off and extraction of the heme with a cold acid alcohol solution and subsequent crystallization from the same solution without change of temperature or evaporation has not been explained. Neither have the differences in crystal structure and combination of the formic and acetic acid hemins.

(*b*) *Chlorohemin.*—In 1900, Nencki and Zaleski (25) prepared a compound which they called "acethemin," by adding fresh defibrinated blood to hot glacial acetic acid containing sodium chloride. Recently Drabkin and Austin (26) have improved this method by using washed blood cells, thereby avoiding the diluting effect of the serum as well as interferences by serum proteins and lipoids. Neither is filtration required as in the earlier process and, therefore, a better yield is obtained.

Blood cells from defibrinated blood were washed four times with a 2 per cent solution of sodium acetate. The cells were added slowly, drop by drop, with vigorous mechanical stirring, to a hot solution (85–90° C.) of glacial acetic acid which had been saturated with sodium chloride at room temperature. The solution became very dark. It was maintained at 85–90° C. and the stirring continued for 30 minutes, then allowed to gradually cool to room temperature. Crystallization had already set in but was not complete for two days. The highly colored supernatant liquid was poured off, the crystals allowed to stand under water over night, then washed twice with 65 per cent alcohol for two days, and finally dried in a vacuum desiccator. Less than 1 g. of chlorohemin is obtained from 100 ml. of cells.

The crystals are purplish-black by reflected light, but, when observed under the microscope, they are from yellow to brown in color, depending upon the size of the crystal. They deposit in the form of elongated monoclinic prisms, as shown in Figure 18. The crystals seem to be quite flat and always appear in the same position on a microscopic slide, indicating that the "b" axis is much shorter than the "a" axis and that it is vertical.

Under polarized light, they show oblique extinction, which is almost parallel to the short edge of the crystal. The diffraction pattern of chlorohemin (Fig. 23),

consists of sharp rings, and a comparison with Figures 21 and 22 shows that this substance is distinctly different from the cent. A photomicrograph of these crystals is shown in Figure 19. The diffraction pattern is similar to that of potassium

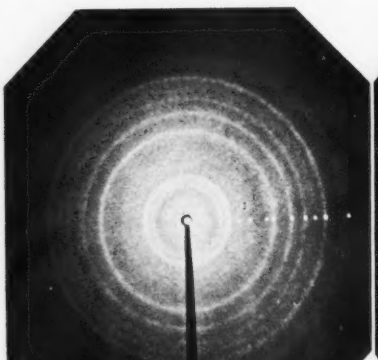

Fig. 21.

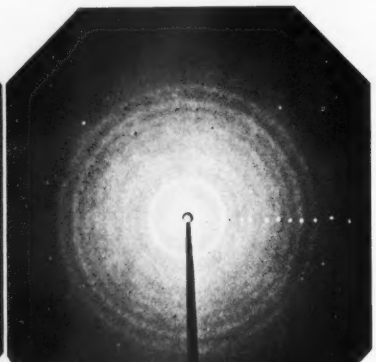

Fig. 22.

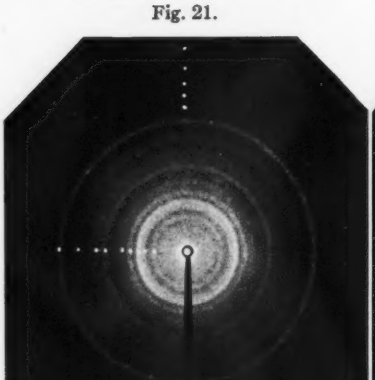

Fig. 23.

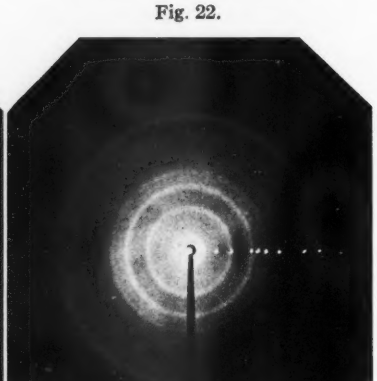

Fig. 24.

Fig. 21. Diffraction pattern of formic acid extracted hemin.
Fig. 22. Acetic acid extracted hemin.
Fig. 23. Chlorohemin.
Fig. 24. Potassium oxyhemin.

hemins prepared by extraction with alcoholic solutions of acetic and formic acids, although in solubility chlorohemin closely resembles the formic acid hemin.

Chlorohemin can be recrystallized by dissolving it in a small amount of a pyridine-chloroform mixture and adding this to a hot solution of glacial acetic and sodium chloride. It is readily soluble in a 2 per cent solution of KOH up to 10 per

oxyhemin (Fig. 24), although the photomicrographs appear quite different due to the size of the potassium oxyhemin crystals.

The interplanar spacings of chlorohemin and their relative intensities are given in Table II.

(*c*) *Potassium Oxyhemin.*—Although it is believed that potassium oxyhemin is merely the potassium salt of chlorohemin,

the name of "potassium oxyhemin" used by Hamsik (27), will be used in this discussion. In his work on the preparation and coupling of the globins, he prepared this substance in crystalline form and was able to couple it with globin to produce a substance whose absorption spectrum was the same as that of alkaline methemoglobin, thus showing its close relationship to hemin.

Blood cells from defibrinated blood were washed four times with 2 per cent acetate solution, hemolyzed with two volumes of water, and centrifuged. To this were added 1.5 volumes of methyl alcohol and then allowed to stand a few hours before filtering. The residue was extracted with 2 per cent KOH in methyl alcohol, which gave a very dark-colored filtrate. Solid KOH was added to the filtrate until the final concentration was about 10 per cent and then set aside in a stoppered flask to crystallize. In only one case, that from hog blood, were large crystals, as shown in Figure 20, obtained. The mother liquor was filtered off and the crystals were washed with a mixture of methyl alcohol and ether (1–3) and finally with ether. The products from cow and horse blood appeared to be a mixture of crystals and a dark amorphous substance, but Figure 24 indicates that it does not affect the sharpness of the diffraction pattern.

The crystals tend to form a felted mass of needles and are usually very small but they show sharp extinction. They are frequently twinned in the form of a cross at an angle of 60 degrees. They are quite soluble in water and can be changed into chlorohemin by adding this solution to hot glacial acetic acid containing sodium chloride, indicating that it is the potassium salt of chlorohemin. In Table II, the relative intensities of the rings and the interplanar spacings represented by them are given.

Since, as it has already been noted, hemoglobin is split in cold solutions of formic acid and potassium hydroxide in alcohol, it seems quite probable that the combination of heme and globin is due to co-ordination valences. Due to the nature of the molecules, there are two other possibilities, salt and amide formation. The former is not likely and an amide linkage is not as easily split as is hemoglobin.

SUMMARY

1. Denatured hemoglobin gives diffraction patterns that are very similar to those of egg albumin correspondingly denatured but the rings are not quite as sharp, which is probably due to the presence of the pigment fraction of hemoglobin.

2. Photomicrographs and diffraction patterns of rat and horse oxy-hemoglobin and horse and pig carbon monoxide hemoglobin are shown. Although the two horse hemoglobins give identical x-ray diffraction patterns, there is a very marked difference between them and the other two, as is also noted in the photomicrographs.

3. The presence of moisture was necessary to maintain the crystalline structure of these proteins.

4. Hemin prepared by extracting hemoglobin with formic acid in alcohol gives a crystalline product, which is the same for rat, cow, pig, and horse hemoglobins, as shown by identical x-ray diffraction patterns. An improvement in the method is given. This hemin was changed into chlorohemin with acetic acid and NaCl.

5. The chlorohemins of the above-mentioned hemoglobins give identical diffraction patterns. Chlorohemin was changed into potassium oxyhemin by dissolving in 2 per cent KOH in methyl alcohol and adding solid KOH. It was recrystallized by dissolving in a small amount of a pyridine-chloroform mixture and adding this to glacial acetic acid containing NaCl.

6. An extraction of alcohol precipitated hemoglobin with 2 per cent KOH in methyl alcohol gave a crystalline product called potassium oxyhemin. The oxyhemins of cow, horse, and pig blood were shown to be identical. It was changed into chlorohemin by adding its water solution to glacial acetic acid containing NaCl.

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THE CIRCULAR LESION OF PULMONARY TUBERCULOSIS[1]

By C. C. BIRKELO, M.D., *and* J. A. KASPER, M.D., Herman Kiefer Hospital, Department of Health, *Detroit, Michigan*

IN the course of study of a large number of chest roentgenograms, one occasionally observes sharply defined round or oval shaped areas of density, usually solitary, and seldom measuring more than four centimeters in diameter. Although in some instances they may be found together with smaller or larger exudative foci in the parenchyma of the lung, and may themselves be multiple, they are in most cases single foci situated in organs showing no other abnormality.

At first sight such circular areas of density resemble neoplastic metastases, but when a study is made of serial films obtained at intervals over a period of months or years, they are found to be remarkably inactive. It is only by obtaining a history strongly supporting tuberculous disease, or by observing excavations accompanied by dissemination of tuberculous infiltrations after a long period of inactivity, that the true nature of the circular lesion is finally established.

Interest in this type of tuberculous lesion dates back to 1925, when Assmann, who first called attention to it, found such isolated circular lesions in the infraclavicular region of the lung. He attributed these lesions to tubercle bacillus implantation and was emphatic in stating that they were not primary since he was not able to observe mediastinal lymph node enlargement associated with them. Following Assmann's first description other observers have contributed to the literature on this subject. In 1931, Albert advanced the opinion that the round foci represented encapsulated tuberculous lesions. A year later, Straub reported on eight cases which he had observed for comparatively long periods of time. He concluded that such foci were of no prognostic significance because he found that some of them could undergo a change, often after a long period of apparent dormancy. He also believed that excavation would be more probable if the lesions that broke down were in direct communication with a bronchus. Straub's belief was that the round focus resulted from an exudative flare-up that later became isolated by connective tissue encapsulation. Klein and Wolff, in 1934, added six more cases to the accumulating literature, five of which showed inactivity of the round foci after one or two years. The other case, which terminated fatally, revealed a lesion which remained stationary for about six months, only to break down and become the cause of a spreading exudative tuberculosis.

This case afforded the autopsy material that showed the characteristic lesion to consist of a chalky caseous substance at its center, encircled by more centrally deposited loose connective tissue and a peripheral dense hyaline connective tissue capsule. This lesion was not considered to be a primary focus and was thought to have had its origin in the bronchus in the course of a bronchogenic spread.

For over five years our interest has been centered on the circular tuberculous focus, our chief purpose being to study its progress and to determine an effective method of treating it.

The 60 cases upon which the present report is based have been selected on the basis of their circular outline. The semicircular and comma-shaped areas of density, so characteristic of the more commonly encountered signs of chronic tuberculosis, were not included in this collection. All cases chosen appear to be tuberculous, some having been so diagnosed by the finding of tubercle bacilli in the sputum, others by obtaining a definite history of contact, and still others showing positive tuberculin reactions.

Most of these cases have been observed for more than a year, some for periods of

[1] Presented before the Radiological Society of North America at the Twenty-second Annual Meeting, at Cincinnati, Nov. 30–Dec. 4, 1936.

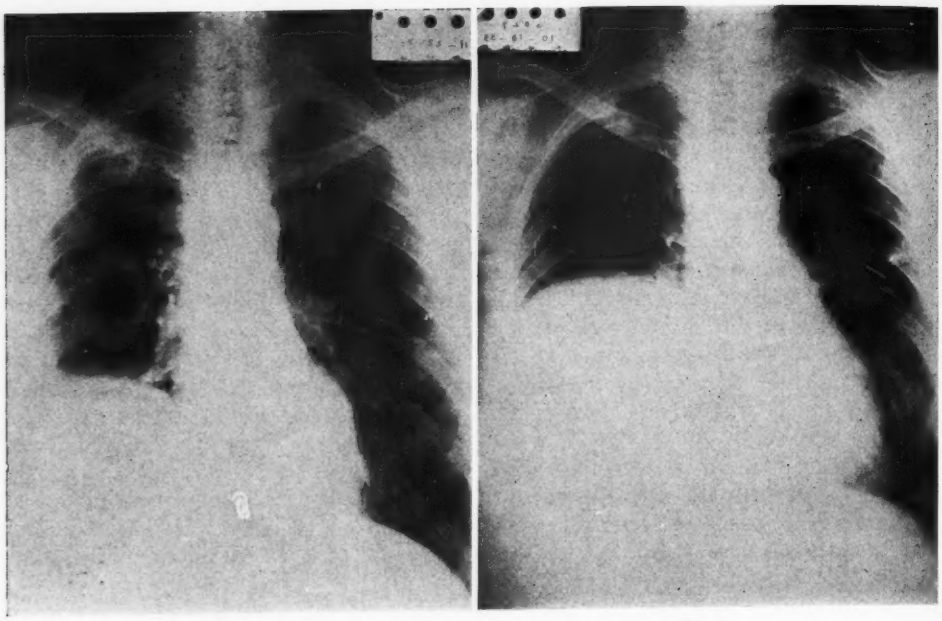

Fig. 1. Fig. 2.

Fig. 1. This case illustrates the type of lesion described in Group I.
Fig. 2. Same case as shown in Figure 1, but three years later.

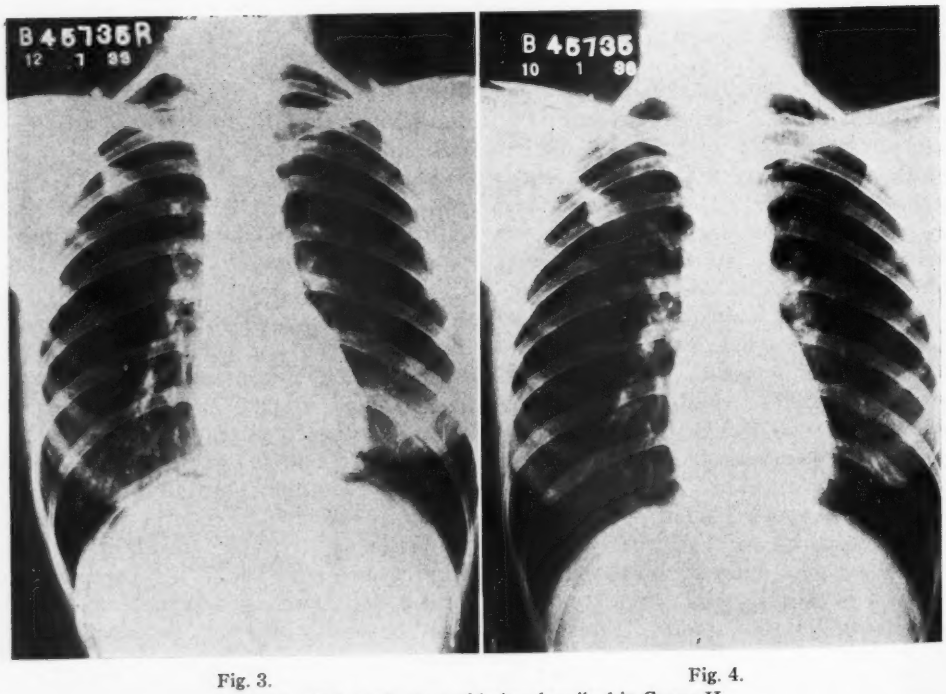

Fig. 3. Fig. 4.

Fig. 3. This is the type of lesion described in Group II.
Fig. 4. The same case as shown in Figure 3, but three years later.

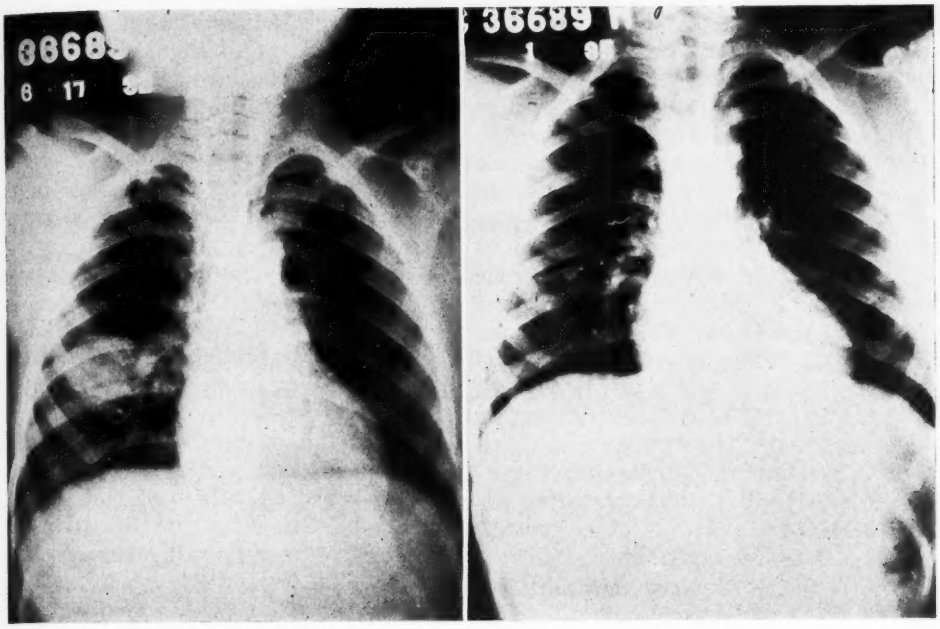

Fig. 5. Fig. 6.

Fig. 5. This is a receding childhood type of lesion described in Group III.
Fig. 6. The same as shown in Figure 5, about three years later.

from five to six years, and a few for six months. While some of the circular lesions were observed to develop from originally diffuse tuberculous infiltration, others were circular at the time of first observation. A small group includes those which appear to represent the final stage of a primary or childhood type of infiltration. Contrary to the belief of the previous observers, it is felt that some circular lesions develop from first infection.

According to our observations, the circular lesions may be divided into the following three groups:

Group I.—This group includes those lesions which have been found to develop from diffuse infiltration. Such lesions are not entirely stationary and may undergo excavation. Most of them, however, show a tendency to become smaller. In this group are included some cases showing other types of tuberculous foci in addition to the characteristic circular lesions. It has been found that the circular lesion is the least likely to play a part in the spreading disease, but may itself show some change simultaneously with changes in the other foci. The lesions in this group, being very unstable, require more careful observation than those of the other two groups.

Group II.—This group includes those lesions which are definitely circular when first discovered. They may be single or multiple, but, in most instances, they are solitary lesions varying in size from 0.5 to 3 cm. in diameter. Most of them are of uniform density and well defined in outline; they are definitely in the parenchyma and not in the pleura as thought by some. Occasionally they excavate and may cause a spread of the tuberculous disease, but this is not usual. These lesions remain stationary for months and years. The lesions in Group II probably represent the well encapsulated type which is least likely to become active.

Group III.—This group includes the receding stage of the childhood type of infiltration. At first, the lesions of this group have been found to be definitely circular;

later, they retrogressed without any collapse therapy. These lesions may be out of place in this discussion, but since they show circular outlines, they are included as part of the whole series of round lesions.

In the light of the observations made, it would appear that the lesions of Group II require only periodic check-up. In the event that excavation should begin, the indication would be for some therapeutic intervention. In this group, three showed evidence of excavation, while 36 remained inactive. The longest period of observation was six years and the shortest, eight months. The cases showing excavation were from among those that were observed for the longer period. However, the excavations in three cases led to complete disappearance of the lesion. Such cases could probably be considered as having their excavating foci in direct communication with bronchi, as suggested by Straub.

The lesions recorded in Group I represent incomplete healing with the possibility of incomplete encapsulation. Since the majority of the 16 cases recorded showed retrogression, it would be justifiable to conclude that their outlook for satisfactory recovery would be good, and that one might expect eventual disappearance of the lesion or complete encapsulation. However, this type of lesion bears more careful observation than that falling in Group II of this classification.

Phrenic surgery was often employed as a precautionary measure. Very few of these cases required pneumothorax and none had to be subjected to thoracoplasty. This group, with the ultimate tendency to encapsulation of their lesions, under no other therapeutic regimen than bed rest, represent the so-called benign type of tuberculosis.

For the third group of cases, namely, those in which the lesions are of the childhood type, no additional suggestions can be advanced, except to emphasize that continued observation of the lesions is a necessity.

THERAPEUTIC RESULTS ACCORDING TO GROUPS

Type	No. of Cases	Phrenic	Pneumothorax	No Treatment	Increase	Decrease	Stationary
I	16	6	4	9	2	8	6
II	39	13	3	26	3	9	27
III	5	0	0	5	0	5	0

SUMMARY

(1) Circular tuberculous lesions in the lungs represent definite types which may be classified into three groups.

(2) The three groups outlined are based upon the mode of development.

(3) The lesions in Group I are found to develop in areas previously showing exudative infiltration, having no definite outline and not of the childhood type. This type of lesion requires more careful observation and proportionately more collapse therapy than lesions of the other two groups.

Group II consists of lesions with definite circular outline when first observed. They may be solid or excavating, but, in the majority of instances, they are very stable and require no collapse therapy.

Group III originates from the primary focus and shows the usual tendency to decrease in size.

(4) Such lesions represent a type of healing in which fibrous encapsulation is the outstanding feature of the pathologic process.

(5) Although circular lesions cannot yet be considered helpful in foretelling the ultimate outcome of the tuberculous lesion, they may be looked upon as being indicative of a relatively benign type of pulmonary tuberculosis.

(6) This report is based on a study of 60 cases and includes 16 in Group I, 39 in Group II, and 5 in Group III.

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DISCUSSION

DR. HENRY KENNON DUNHAM (Cincinnati, Ohio): I am very much pleased with this presentation and anything I may say must not be construed as criticism but approval. And yet, when the Doctor speaks of benign tuberculosis, that is a good deal like a red rag to a bull to me because I don't believe that any kind of tuberculosis that really is honest-to-God tuberculosis is benign.

It does get well sometimes—becomes arrested—but to classify any form of tuberculosis as benign—well, it's hard on my mentality.

The three groups of lesions which the essayist describes are clear.

The first group corresponds to the lesions which I originally described as fans. Pulmonary exudate has been absorbed and the repair tissue has contracted the residue into a spherical lesion.

Last Sunday at the Sanatorium we reviewed a case in which a spherical lesion had contracted around an arrested area of tuberculosis bronchopneumonia.

Thus, many spherical areas of increased pulmonary density can be explained by absorption of pulmonary exudate and contraction of scar tissue. Several such cases can be seen in the exhibit in the other rooms.

The other two groups are not so easily explained, understood, or diagnosed. Some of them, as the essayist has said, break down and are easily proved tuberculous. Those which do not are in question and I think it unsound to diagnose them tuberculous lesions. One fan or one density may be tuberculous but two or more such densities suggesting different age are necessary to clinch an x-ray diagnosis of tuberculosis. Certainly a positive tuberculin reaction with one such density is not enough upon which to base a diagnosis of tuberculosis.

I hope that these densities in the future will be described as spherical rather than circular because stereoscopically they can be seen to be round.

It is a pleasure to add Dr. Ewing's name to the literature because he was the first to call to my attention these round lesions, some of which he had proven to be tuberculous. This was in 1916 or 1917.

The term "first infection" should, in my opinion, be called "first infections," because we do not know what infection was first. If we accept the definition of allergy given by Dr. Krouse, then allergy begins when we have had enough first infections to create an allergic state. A positive tuberculin reaction may not indicate an allergic state. An allergic state has developed when an individual has had enough first infection to cause a new tuberculous infection to produce an inflammatory reaction at the point of inoculation.

Reinke's primary infection was a lesion of which we could have no clinical nor pathological proof but which existed nevertheless.

The point I wish you to consider is that when such terms as "first infection," "allergy," "hypersensitiveness," and "immunity" are used, we really require the author's definition before we can fully understand his diction.

DR. BIRKELO (closing): I have very little to add except to thank Dr. Dunham for his generous discussion. I knew I would get a good discussion from him.

I feel the same as he does about benignity of tuberculosis. I don't think there is such a thing but, relatively speaking, I think the circular lesion is the most benign tuberculous lesion I know anything about.

As far as the lesion being spherical, that is, perhaps, true, but we selected the other name because most of our work is done with flat films.

I didn't find anything in the literature written by Dr. Ewing on this subject. I am not describing anything new. My purpose in taking up this subject was to attempt to standardize the treatment of this type of lesion.

THE EFFECT OF ROENTGEN RAYS ON THE GROWTH OF MOUSE SARCOMA 180 IRRADIATED *IN VIVO*

By KANEMATSU SUGIURA, D.M.Sc., *New York City*

From the Huntington Fund for Cancer Research, Memorial Hospital

IN a previous study (1) the effect of 200 kv. roentgen rays on Mouse Sarcoma 180 *in vitro* was investigated. It was found that the viability of the mouse sarcoma was completely destroyed by an exposure to a dose of about 2,800 roentgens of filtered roentgen rays.

It was further shown in this institution that the injurious action of filtered roentgen rays on the proliferating capacity of sarcoma cells was decidedly increased when the tumor tissues were irradiated upon the surface of a paraffin phantom. The back-scatter obtained by this method was found to be 30 per cent (2). Later we measured the depth dose by means of the transplantable tumor, using a paraffin phantom. The percentage depth dose at 2, 6.7, and 9.8 cm. was found to be 97, 86, and 54, respectively (2). These values agree reasonably well with the depth doses determined by ionization measurements made under similar conditions.

In the irradiation of the tumor tissues *in vitro*, they are completely isolated from the surrounding normal tissues, blood vessels, tissue fluid, etc. Therefore, it is possible to observe the direct action only. However, from studying the biological effects of roentgen rays *in vivo* and comparing the results with those obtained by experiments *in vitro*, it may be possible to calculate the extent of the direct and indirect actions of radiation upon living cells. The following experiments were carried out with the object of testing this supposition.

MATERIALS AND METHODS

The Mouse Sarcoma 180 was selected for the present study, the behavior of which in mice has been reported elsewhere. It may be of interest, however, to summarize its manner of development, since this may have a bearing upon the present investigation. A graphic illustration of a number of more or less typical examples of the progress of normal tumor implants in animals may show this development clearly (Fig. 1).

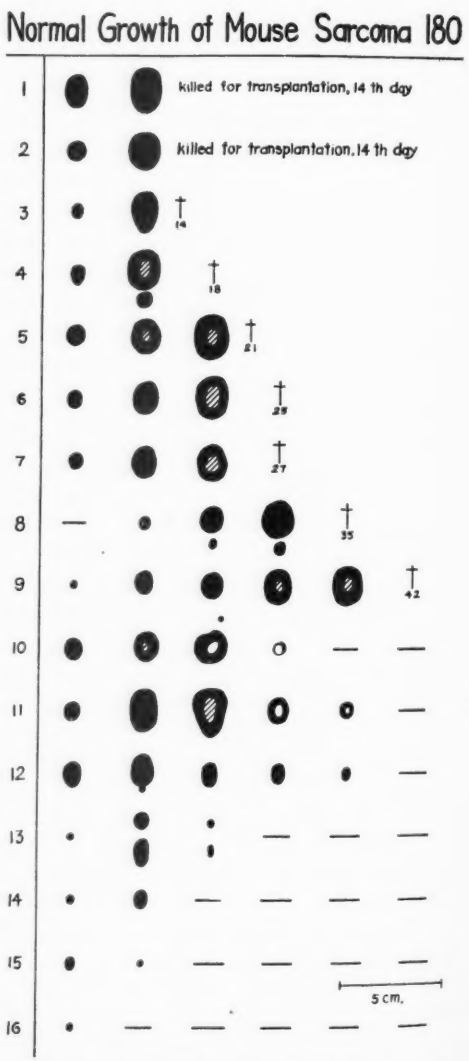

Fig. 1. Progress of normal tumor implants in white mice.

When pieces of Mouse Sarcoma 180, each weighing about 6 mg., and measuring about $(2 \text{ mm.})^3$ are inoculated subcutaneously in the lateral thoracic region by trocar, many of these transplants grow in spherical or in ovoid form, becoming flattened on their deeper aspect during the first week. As the tumors grow larger, many of them develop pressure necrosis at the subcutaneous parts of the tumors as early as the second week, and subsequently cause the deaths of the animals from toxemia, septicemia, and nutritional failure in about three weeks from the time of transplantation (Fig. 1, Nos. 4, 5, 6, 7). Some of the large tumors ulcerate, become infected and slough, and eventually regress and disappear completely (Fig. 1, Nos. 10, 11), while others grow normally for two to three weeks and then regress (Fig. 1, Nos. 12, 13, 14). The former cases we call spontaneous cures, and the latter cases, spontaneous regressions. All of these cases are considered as positive "takes." However, in a case like No. 14, in which the transplant grew very rapidly for two weeks and then absorbed, one must ascertain whether or not the apparent growth is due to inflammatory reaction or to a true tumor. If the growth is inflammatory in nature, it should not be included as a positive take. Some transplants proliferate in the animals for several days, and then regress and are absorbed. If they are completely absorbed within two or three weeks, they are considered as negative transplants (Fig. 1, Nos. 15, 16).

Subcutaneous inoculations of tumor into healthy young adult white mice, males and females, weighing generally from 23 to 30 gm., were carried out by the usual trocar method, the tumor materials being selected from rapidly growing tumors which had not ulcerated. The tumors were about two weeks old (Fig. 1, Nos. 1, 2). The animals were fed upon Purina laboratory chows and lettuce, with as much fresh water as they would take.

During the past six months we had made over 600 normal tumor implantations and found that in the majority of the series the tumor "takes" were 100 per cent and seldom below 90 per cent, the average takes being 99 per cent. The transplants showed occasional spontaneous regression, such cases representing about 4 per cent of the positive growths. However, spontaneous absorption (spontaneous cure + spontaneous regression) was about 11 per cent.

EFFECT OF ROENTGEN RAYS ON THE HEALTH OF WHITE MICE

As a preliminary study, we have determined the amount of radiation tolerated by the mouse when given as a single massive dose.

Young healthy adult white mice, males and females, weighing generally from 23 to 30 gm., were fastened on a stiff pasteboard, two at a time as shown in Figure 2. In this manner the mice remained in a fixed position during the irradiation with their backs touching the pasteboard.

The radiation was supplied by a standard water-cooled Coolidge roentgen tube under the following conditions: 200 kv., 30 ma., 0.5 mm. copper, and 1.6 mm. aluminum filter, 50 cm. distance from the target to the ventral skin surface of the body. At this point, the intensity of the beam measured in air was found to be 59 roentgens per minute.

A careful record was kept of the physical condition, body weight, and the duration of life of these irradiated mice. The biological effects of the filtered roentgen rays on mice may be briefly summarized as follows: A dose of 250 r or less had no harmful influence upon the nutrition of the mice. The animals grew normally and maintained excellent health during the experimental period of about two months. Doses of 350 and 400 r generally prevented gain in body weight. Some lost weight slightly during the first two weeks, but maintained their weight thereafter. With the former dose none died, but with the latter dose 18 per cent of animals died. With a dose of 500 r, the animals lost weight and 71 per cent of them died, some

as early as the ninth day; others lived during the experimental period of about two months. However, when a dose of 750 r or more was given, all animals showed marked nutritional disturbance, continued loss of body weight, and all died within 18 days, the shortest interval being the third day, this following a dose of 1,000 r or over.

TABLE I.—EFFECT OF ROENTGEN RAYS (200 KV., 30 MA., 0.5 MM. CU + 1.6 MM. AL FILTER) UPON THE HEALTH OF WHITE MICE

No. Animals Used	Dose in Roentgens	Remarks
6	2830	2 mice died on third day; 4 mice died on fourth day
8	1500	2 mice died on third day; 4 mice died on fourth day; 2 mice died on fifth day
12	1000	4 mice died on third day; 2 mice each died on fourth, fifth, sixth, and eighth day
16	750	2 mice each died on ninth, tenth, twelfth, and eighteenth day; 4 mice each died on thirteenth and fourteenth day
21	500	2 mice each died on ninth, thirteenth, and fourteenth day; 4 mice each died on tenth and eleventh day; 1 mouse died on nineteenth day; 6 mice survived
22	400	2 mice died on fourteenth day; 1 mouse each died on twentieth and twenty-fifth day; 18 mice survived
12	350	All survived
10	250	All survived
11	100	All survived

EFFECT OF ROENTGEN RAYS ON MOUSE SARCOMA 180

The foregoing experiments showed the effect of radiation on the entire body of the animal whose total body volume[1] was approximately 28 c.c. With these conditions a dose of 350 r did not kill any mice; with a dose of 400 r, 18 per cent of mice died. As irradiation continued the lethal effect on mice greatly increased. Thus the doses of 500 and 750 r produced 71 and 100 per cent lethal results, respectively. Therefore, a dose of 400 r is just about on the borderline between the lethal and sub-lethal.

When the area irradiated is about 2.9 sq. cm., so that a limited volume of the body, 4.8 c.c., is irradiated on the right or left lateral thoracic region, then the dosage can be increased to about 3,000 r without much nutritional disturbance. Some animals, however, died from x-ray anemia some weeks after irradiation.

The experimental procedure was as follows: Fragments of Mouse Sarcoma 180 were inoculated subcutaneously into young adult mice in the right or left lateral thoracic region by trocar. When tumor grafts had grown from six to ten days to establish a suitable size, they were submitted to roentgen-ray irradiation. Two tumor-bearing animals were fastened side by side on a stiff pasteboard as shown in Figure 2. A specially constructed lead shield 5 mm. thick with celluloid 1 mm. thick attached, and having a hole 2 × 2.9 cm. in the center, was then placed over these animals with their ventral hair touching the celluloid as shown in Figure 3. In this way all parts of the animal except the tumor and its surrounding normal tissues were protected from radiation. Then the pasteboard holding the tumor-bearing animals was placed directly under the roentgen tube with a target-skin distance of 50 cm., and subjected to radiation under the conditions previously described, intensity being 59 r per minute. The absorption of radiation through 0.3 mm. thickness of skin and hair of a mouse is negligible in this case.

The development of the tumors in the animals was recorded graphically by measuring them every week by means of calipers.

The results obtained from irradiation of mouse sarcomas of various sizes are presented in Table II. In this table are included all observations, positive and negative, in the hope of finding the minimum lethal dose expressed in roentgens for the Mouse Sarcoma 180 in animals. In the second column of the table the sizes of the

[1] The total body volume was determined by submerging the entire body in water contained in a small graduated cylinder.

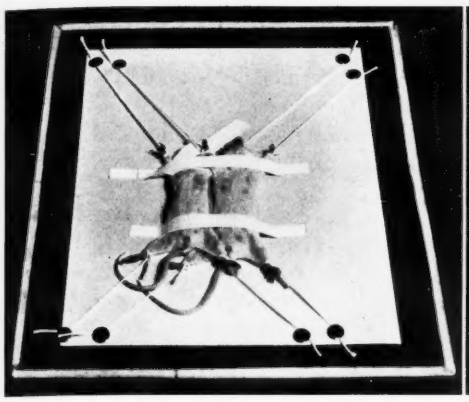

Fig. 2.

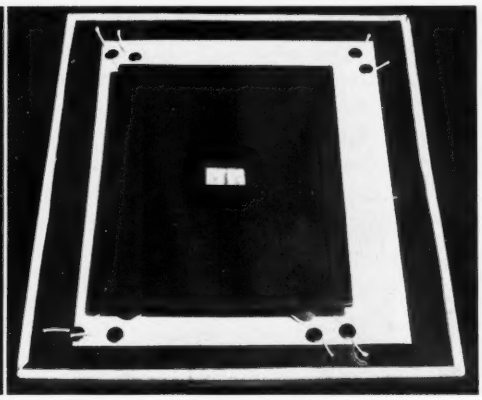

Fig. 3.

Fig. 2. Method of fastening mice to animal board for irradiation.

Fig. 3. Two tumors were irradiated *in vivo* through a hole slightly larger than the cross-section of the tumor in a lead shield 5 mm. thick.

tumors are denoted by the measurements of lengths, widths, and thicknesses. In the table the complete absorption of the tumors is indicated by a plus sign (+) in the fifth column, while the continuation of tumor growth is indicated by a minus sign (−). In the last column we have given a brief account of the behavior of the irradiated tumors. The data are arranged according to the decreasing duration of tissue exposure.

It will be seen that the destruction of the malignant growths was easily accomplished by the radiation from filtered roentgen rays. A dose of 1,480 r or over regularly produced a definite inhibition in the growth of the Mouse Sarcoma 180 and subsequently complete retrogression in about twenty-four days. Even in many of the negative cases, the tumors remained stationary during the first two weeks after irradiation, but later resumed normal growth and killed the hosts, or ulcerated and disappeared.

It may be of interest to mention that the irradiated tumor actually increased in size during the first week after irradiation, even with a large dose of 1,500–3,000 r. The enlargement of the tumor tissue may have been due merely to edema rather than to actual cell proliferation. Histologic examination of a number of the irradiated tumor tissues revealed numerous swollen cells and intercellular edema.

Progressively growing tumors are colored light pink; after irradiation, the color changes to a deep purple, while subsequently the tumor becomes gradually pale and bloodless. During this period it is decreasing in size.

None of the 74 animals cured of their tumors by roentgen rays showed local recurrences. A small number of cured animals showed tumors along the course of the trocar insertion (an area well protected from radiation by the lead shield) some days after irradiation. These tumors either continued to grow normally, or regressed completely, the regression often paralleling that of the irradiated primary tumor.

The following reactions were produced in the skin. With doses of from 100 to 750 r, there was no epilation. With a dose of 1,000 r, no changes were visible for the first six weeks after exposure, but toward the end of the seventh week a slight epilation of the irradiated area occurred. With a dose of 1,500 r, partial epilation occurred at the fifth week, followed by a gradual return of hair. Doses from 1,770 to 3,540 r showed a gradual increase in the complete-

ness of the epilation, permanent in some cases, but temporary in others. Under the stated condition of irradiation neither necrosis nor ulceration of the skin was produced.

In an attempt to establish a minimum curative dose in roentgens for the Mouse Sarcoma 180 *in vivo* the results presented in Table II are grouped as in Table II-*A*. From this arrangement it is evident that no tumor regressed with a minimum dose of less than 500 r, and very few with less than 750 r. With a dose of 1,000 r, about half of the cases showed regressions. With more than 1,500 r, regression occurred in almost 100 per cent of cases in which the masses were not more than 1.5 cm. in diameter. A graphic illustration of a number of more or less typical examples of the progress of irradiated and non-irradiated tumors may show this point more clearly (Fig. 4).

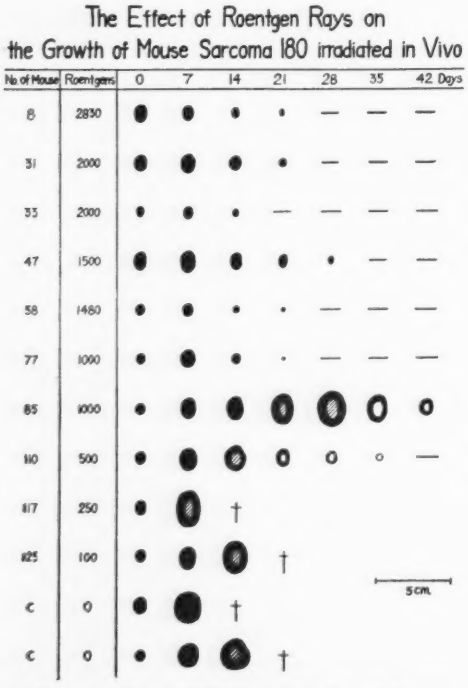

Fig. 4. The proliefrating capacity of Mouse Sarcoma 180 was completely inhibited with a dose of 1,500 r or more. On the other hand, a dose of 1,000 r or less was insufficient for the complete destruction of the sarcoma. Age of these tumors was seven days. C represents unirradiated tumors.

In connection with the present study, a number of observations were made with Mouse Sarcoma 180 fragments irradiated in air to determine whether or not the radiosensitivity of the tumor had remained the same as had previously been determined.

This study included three groups of experiments, involving a total of 96 implants. The apparatus, materials, technic, and the conditions of irradiation were the same as those previously described.

The results obtained from this procedure showed that 48 minutes' exposure (about 2,830 r) of the tumor fragments to filtered radiation prevented 83 per cent of them from growth (average of 60, 90, and 100 per cent inhibition) instead of 100 per cent as in previous experiments (1, 2). Since biological experiments of this sort are subject to experimental errors of considerable magnitude, it is not possible at present to state that the difference is sigficant. The viability of the transplants, however, was completely destroyed by 49.5 and 51 minutes' exposure (about 2,920 and 3,000 r) in the present study.

TABLE II–A.—RESULTS OF IRRADIATION OF TUMORS 1.5 CENTIMETERS OR LESS IN DIAMETER (6 TO 10 DAYS IN AGE) *IN VIVO*

Dose in Roentgens	Positive Reaction	Negative Reaction	Percentage of Cure
100	0	8	0
250	0	8	0
500	0	18	0
750	2	8	20
1,000	6	6	50
1,060	4	4	50
1,480	11	1	92
1,500	7	2	78
1,770	6	2	75
2,000	10	0	100
2,540	6	0	100
2,830	16	0	100
3,240	4	0	100
3,540	2	0	100

DISCUSSION

In comparing the results obtained from experiments *in vitro* and *in vivo* with a transplantable mammalian tumor it will be noted that the lethal dose for Mouse Sarcoma 180 *in vitro* for well-filtered roent-

TABLE II-B.—EFFECT OF ROENTGEN RAYS (200 KV., 30 MA., 0.5 MM. CU + 1.6 MM. —BL FILTER) UPON THE GROWTH OF MOUSE SARCOMA 180 IN ANIMALS

No. of Animal	Dimensions of Tumor (mm.)	Duration of Exposure (minutes)	Dose in Roentgens	Results of Irradiation	Remarks
1	10.5 × 10 × 7	60	3,540	+	Tumor rapidly retrogressed; complete absorption in 21 days.
2	6.5 × 6 × 5	60	3,540	+	Tumor slowly retrogressed; complete absorption in 33 days.
3	4.7 × 4.5 × 3	55	3,240	+	Tumor rapidly retrogressed; complete absorption in 21 days.
4	7 × 7 × 5	55	3,240	+	Tumor rapidly retrogressed; complete absorption in 21 days.
5	5.4 × 4.5 × 2	55	3,240	+	Tumor rapidly retrogressed; complete absorption in 19 days.
6	15.2 × 12 × 8	55	3,240	+	Tumor slowly retrogressed; complete absorption in 30 days.
7	4 × 4.5 × 3	48	2,830	+	Tumor rapidly retrogressed; complete absorption in 21 days.
8	10.5 × 6.5 × 5	48	2,830	+	Tumor slowly retrogressed; complete absorption in 29 days.
9	10.8 × 8.5 × 7	48	2,830	+	Tumor slowly retrogressed; complete absorption in 35 days.
10	3.1 × 2.5 × 2	48	2,830	+	Tumor rapidly retrogressed; complete absorption in 18 days.
11	6.5 × 5.5 × 3	48	2,830	+	Tumor rapidly retrogressed; complete absorption in 21 days.
12	3.2 × 2.2 × 1	48	2,830	+	Tumor slowly retrogressed; complete absorption in 25 days.
13	3.8 × 2.2 × 2	48	2,830	+	Tumor rapidly retrogressed; complete absorption in 14 days.
14	4.8 × 5 × 3	48	2,830	+	Tumor slowly retrogressed; complete absorption in 30 days.
15	10 × 9 × 7	48	2,830	+	Tumor rapidly retrogressed; complete absorption in 21 days.
16	10.5 × 9 × 8	48	2,830	+	Tumor slowly retrogressed; complete absorption in 35 days.
17	7.2 × 6.5 × 4	48	2,830	+	Tumor slowly retrogressed; complete absorption in 28 days.
18	5.1 × 5 × 4	48	2,830	+	Tumor rapidly retrogressed; complete absorption in 21 days.
19	7 × 6.5 × 3	48	2,830	+	Tumor rapidly retrogressed; complete absorption in 14 days.
20	11.5 × 9.5 × 7	48	2,830	+	Tumor slowly retrogressed; complete absorption in 30 days.
21	4 × 3 × 2	48	2,830	+	Tumor rapidly retrogressed; complete absorption in 19 days.
22	3.5 × 2.8 × 2	48	2,830	+	Tumor rapidly retrogressed; complete absorption in 15 days.
23	9.5 × 7.8 × 5	43	2,540	+	Tumor rapidly retrogressed; complete absorption in 21 days.
24	8.1 × 7.5 × 5	43	2,540	+	Tumor slowly retrogressed; complete absorption in 28 days.
25	15.2 × 12 × 8	43	2,540	+	Tumor slowly retrogressed; complete absorption in 35 days.
26	8.9 × 7.4 × 5	43	2,540	+	Tumor slowly retrogressed; complete absorption in 28 days.
27	5.2 × 4.5 × 3	43	2,540	+	Tumor rapidly retrogressed; complete absorption in 21 days.
28	5.8 × 3.1 × 2	43	2,540	+	Tumor rapidly retrogressed; complete absorption in 14 days.
29	7.2 × 6.5 × 4	34	2,000	+	Tumor rapidly retrogressed; complete absorption in 21 days.
30	8.5 × 7 × 5	34	2,000	+	Tumor rapidly retrogressed; complete absorption in 21 days.
31	10 × 8 × 6	34	2,000	+	Tumor slowly retrogressed; complete absorption in 28 days.
32	4.5 × 3 × 1.5	34	2,000	+	Tumor slowly retrogressed; complete absorption in 25 days.
33	7.2 × 4.5 × 2	34	2,000	+	Tumor rapidly retrogressed; complete absorption in 21 days.

+ indicates cure of tumor; − indicates continued growth of tumor.

(Cont'd on next page)

No. of Animal	Dimensions of Tumor (mm.)	Duration of Exposure (minutes)	Dose in Roentgens	Results of Irradiation	Remarks
34	4.5 × 3.7 × 2	34	2,000	+	Tumor rapidly retrogressed; complete absorption in 21 days.
35	3.5 × 2 × 1	34	2,000	+	Tumor rapidly retrogressed; complete absorption in 18 days.
36	6 × 5.5 × 3	34	2,000	+	Tumor rapidly retrogressed; complete absorption in 19 days.
37	4.8 × 3.5 × 2	34	2,000	+	Tumor slowly retrogressed; complete absorption in 33 days.
38	14.5 × 9.7 × 7	34	2,000	+	Tumor rapidly retrogressed; complete absorption in 35 days.
39	6.2 × 6.4 × 2	30	1,770	+	Tumor rapidly retrogressed; complete absorption in 21 days.
40	7.8 × 5 × 2.5	30	1,770	+	Tumor rapidly retrogressed; complete absorption in 21 days.
41	5.5 × 5.3 × 4	30	1,770	+	Tumor slowly retrogressed; complete absorption in 29 days.
42	8 × 7 × 5	30	1,770	+	Tumor slowly retrogressed; complete absorption in 35 days.
43	10.9 × 9 × 7	30	1,770	+	Tumor slowly retrogressed; complete absorption in 28 days.
44	7.5 × 6.5 × 3	30	1,770	+	Tumor rapidly retrogressed; complete absorption in 21 days.
45	6.5 × 6.4 × 5	30	1,770	−	Tumor growth stopped for 12 days; then normal growth.
46	3.5 × 2.5 × 2	30	1,770	−	Tumor growth stopped for 14 days; then normal growth.
47	11 × 7.3 × 5	25.4	1,500	+	Tumor slowly retrogressed; complete absorption in 30 days.
48	6.2 × 5.5 × 2.5	25.4	1,500	+	Tumor rapidly retrogressed; complete absorption in 21 days.
49	7.8 × 7.5 × 4	25.4	1,500	+	Tumor rapidly retrogressed; complete absorption in 21 days.
50	8.1 × 7.2 × 5	25.4	1,500	+	Tumor slowly retrogressed; complete absorption in 28 days.
51	8.2 × 8 × 5	25.4	1,500	+	Tumor slowly retrogressed; complete absorption in 28 days.
52	5 × 4 × 2	25.4	1,500	+	Tumor rapidly retrogressed; complete absorption in 21 days.
53	6.5 × 5.8 × 3	25.4	1,500	+	Tumor rapidly retrogressed; complete absorption in 18 days.
54	6.5 × 6.2 × 4	25.4	1,500	−	Tumor continued to grow.
55	9 × 7.5 × 4	25.4	1,500	−	Tumor continued to grow.
56	3.1 × 2.5 × 1	25	1,480	+	Tumor rapidly retrogressed; complete absorption in 14 days.
57	5.5 × 5.5 × 3	25	1,480	+	Tumor rapidly retrogressed; complete absorption in 21 days.
58	6.5 × 5.2 × 3	25	1,480	+	Tumor slowly retrogressed; complete absorption in 26 days.
59	10 × 7.5 × 6	25	1,480	+	Tumor slowly retrogressed; complete absorption in 28 days.
60	7.8 × 7 × 5	25	1,480	+	Tumor rapidly retrogressed; complete absorption in 21 days.
61	9.5 × 7.3 × 6	25	1,480	+	Tumor rapidly retrogressed; complete absorption in 21 days.
62	8.5 × 7 × 4	25	1,480	+	Tumor slowly retrogressed; complete absorption in 28 days.
63	7.2 × 5 × 3	25	1,480	+	Tumor rapidly retrogressed; complete absorption in 21 days.
64	3 × 3 × 2	25	1,480	+	Tumor rapidly retrogressed; complete absorption in 14 days.
65	3.5 × 3 × 2	25	1,480	+	Tumor rapidly retrogressed; complete absorption in 14 days.
66	4.7 × 4.5 × 3	25	1,480	+	Tumor rapidly retrogressed; complete absorption in 21 days.
67	4.5 × 4.5 × 3	25	1,480	−	Tumor continued to grow.
68	3.5 × 3.1 × 2	18	1,060	+	Tumor rapidly retrogressed; complete absorption in 14 days.
69	5 × 4.2 × 2	18	1,060	+	Tumor slowly retrogressed; complete absorption in 47 days.
70	9 × 6.2 × 4	18	1,060	+	Tumor slowly retrogressed; complete absorption in 28 days.

(Cont'd on next page)

No. of Animal	Dimensions of Tumor (mm.)	Duration of Exposure (minutes)	Dose in Roentgens	Results of Irradiation	Remarks
71	2.5 × 2.5 × 1	18	1,060	+	Tumor slowly retrogressed; complete absorption in 28 days.
72	12.2 × 5.3 × 3	18	1,060	−	Tumor continued to grow.
73	4 × 2.7 × 2	18	1,060	−	Tumor continued to grow.
74	6.5 × 5 × 3	18	1,060	−	Tumor continued to grow.
75	7 × 5 × 3	18	1,060	−	Tumor continued to grow.
76	6.5 × 4.3 × 3	17	1,000	+	Tumor rapidly retrogressed; complete absorption in 21 days.
77	6.2 × 5.2 × 3	17	1,000	+	Tumor slowly retrogressed; complete absorption in 22 days.
78	6.0 × 5.8 × 3.5	17	1,000	+	Tumor slowly retrogressed; complete absorption in 39 days.
79	11.5 × 7.5 × 5	17	1,000	+	Tumor slowly retrogressed; complete absorption in 35 days.
80	9 × 6.7 × 5	17	1,000	+	Tumor slowly retrogressed; complete absorption in 24 days.
81	5 × 5 × 2	17	1,000	+	Tumor rapidly retrogressed; complete absorption in 21 days.
82	3.5 × 2.7 × 2	17	1,000	−	Tumor continued to grow.
83	6.2 × 5.1 × 3	17	1,000	−	Tumor continued to grow.
84	4.9 × 5 × 2.5	17	1,000	−	Tumor continued to grow.
85	6.7 × 6.5 × 5	17	1,000	−	Tumor continued to grow.
86	9.4 × 7.5 × 5	17	1,000	−	Tumor continued to grow.
87	4 × 4 × 3	17	1,000	−	Tumor continued to grow.
88	6.4 × 4.3 × 3.5	12.7	750	+	Tumor slowly retrogressed; complete absorption in 29 days.
89	6.8 × 6.5 × 4	12.7	750	+	Tumor slowly retrogressed; complete absorption in 28 days.
90	4.9 × 5 × 3	12.7	750	−	Tumor continued to grow.
91	7 × 5.5 × 4	12.7	750	−	Tumor continued to grow.
92	7.3 × 5.5 × 3	12.7	750	−	Tumor continued to grow.
93	6.2 × 5.5 × 3	12.7	750	−	Tumor continued to grow.
94	4.8 × 4 × 3	12.7	750	−	Tumor continued to grow.
95	7.2 × 6.4 × 4	12.7	750	−	Tumor continued to grow.
96	7 × 6.2 × 4	12.7	750	−	Tumor continued to grow.
97	3.2 × 2.5 × 2	12.7	750	−	Tumor continued to grow.
98	4 × 3.2 × 2	8.5	500	−	Tumor continued to grow.
99	5.2 × 4.8 × 3	8.5	500	−	Tumor continued to grow.
100	5.8 × 5.3 × 4	8.5	500	−	Tumor continued to grow.
101	7 × 6.3 × 4	8.5	500	−	Tumor continued to grow.
102	7.5 × 4.5 × 3	8.5	500	−	Tumor continued to grow.
103	7 × 6.5 × 4	8.5	500	−	Tumor continued to grow.
104	5 × 5 × 3	8.5	500	−	Tumor continued to grow.
105	3.5 × 3 × 2	8.5	500	−	Tumor continued to grow.
106	5.5 × 5.2 × 4	8.5	500	−	Tumor continued to grow.
107	6.5 × 5.5 × 3	8.5	500	−	Tumor continued to grow.
108	5.4 × 5.1 × 2.5	8.5	500	−	Tumor continued to grow.
109	6.5 × 5 × 2.5	8.5	500	−	Tumor continued to grow.
110	7.1 × 7 × 4	8.5	500	−	Tumor continued to grow.
111	6.1 × 6.4 × 3	8.5	500	−	Tumor continued to grow.
112	6.2 × 4.8 × 3	8.5	500	−	Tumor continued to grow.
113	7.4 × 5 × 4	8.5	500	−	Tumor continued to grow.
114	2.8 × 2.2 × 2	8.5	500	−	Tumor continued to grow.
115	4 × 4 × 2	8.5	500	−	Tumor continued to grow.
116	8 × 6 × 4	4.2	250	−	Tumor continued to grow.
117	7.2 × 4.7 × 3	4.2	250	−	Tumor continued to grow.
118	7.2 × 4.2 × 2	4.2	250	−	Tumor continued to grow.
119	3 × 2.2 × 1	4.2	250	−	Tumor continued to grow.
120	6.2 × 6 × 4	4.2	250	−	Tumor continued to grow.
121	5.8 × 5 × 3	4.2	250	−	Tumor continued to grow.
122	3 × 2.5 × 1	4.2	250	−	Tumor continued to grow.
123	8 × 6.2 × 4	4.2	250	−	Tumor continued to grow.
124	6.2 × 4.4 × 3	1.7	100	−	Tumor continued to grow.
125	7 × 6.2 × 4	1.7	100	−	Tumor continued to grow.
126	5.8 × 3.1 × 2	1.7	100	−	Tumor continued to grow.
127	3 × 2.2 × 1	1.7	100	−	Tumor continued to grow.
128	3.5 × 3 × 2	1.7	100	−	Tumor continued to grow.
129	7.2 × 6.8 × 3	1.7	100	−	Tumor continued to grow.
130	3.5 × 3.5 × 2	1.7	100	−	Tumor continued to grow.
131	7.2 × 7 × 4	1.7	100	−	Tumor continued to grow.

gen rays is between 2,800 and 3,000 r, while the lethal dose for the same tumor *in vivo* is found to be about 1,500 r.

The present results are in accord with the findings of Murphy, Maisin, and Sturm (3), who, working with spontaneous mammary cancer in mice found that 48 out of 50 grafts which were subjected to an erythema dose of x-rays *in vitro* grew progressively when inoculated intracutaneously in the original animals, or 96 per cent growth. On the other hand, when untreated grafts which had grown for about ten days in the original animals, were given a like dose of x-rays *in situ*, there followed a prompt disappearance of the tumor in 38 of 50 mice (76 per cent). It has been shown by Russ and Scott (4) that the cell-free filtrate of the Rous chicken sarcoma is very resistant to x-rays when the exposure is made *in vitro*. Even five times the lethal dose for Jensen rat sarcoma, Twort mouse carcinoma and Mouse Sarcoma 180 was unable to affect the infectivity of the extract. But Mottram (5) has pointed out that when the Rous chicken sarcoma is growing in the animal, exposure to the beta rays of radium will bring about disappearance of these tumors with doses not much greater than those necessary to bring about disappearance of rat and mouse tumors.

Such wide differences in radiosensitivity would indicate that the destructive effect of radiation upon tumors *in vivo* is due to a combination of direct action on the tumor cells, and the reaction of the surrounding tissues.

In this connection it is of great importance to mention the findings of Ewing with human material (6). Ewing states:

> "It is clear that the reaction of the tissues is an essential factor in the curative process. Under some circumstances, when this reaction fails, no amount of radiation succeeds in killing the tumor cells . . . the most detailed knowledge we possess indicates clearly that the curative action is not the result of a direct effect exclusively upon the tumor cells, but involves especially a peculiar reaction of the normal or invaded tissues."

In order to ascertain whether or not the increased radiosensitivity of tumor cells *in vivo* is due to the effect of scattered radiation the following experiments were made.

When tumor grafts had grown for about seven days in animals, they were irradiated with a dose of 2,830 r or 1,500 r in the same manner as that previously described. At the end of definite intervals of time the irradiated tumors were removed from the animals and tumor fragments were inoculated into normal animals in the usual way. It was found that none of the tumors which were extirpated immediately after irradiation with a dose of 2,830 r grew in animals. On the other hand, if the tumors were irradiated with a dose of 1,500 r, then removed immediately and inoculated into normal animals, they grew progressively in about 80 per cent as in the case of tumor fragments irradiated *in vitro* with the same dose of roentgen rays. But, if the irradiated tumors were allowed to remain in the irradiated area of animals for twenty-four hours, then removed and inoculated into normal animals, about 50 per cent of them produced growth. The viability of the irradiated tumors showed a gradual decrease upon remaining in the hosts. Thus when irradiated tumors (with a dose of 1,500 r) were removed from animals five days after irradiation and inoculated into normal animals, there followed only 20 per cent takes, while complete inhibition occurred if the irradiated tumors had remained in the hosts seven days or longer before re-implantation.

In the course of the investigation we also have determined the transplantability of Mouse Sarcoma 180 into irradiated areas in mice. A small portion of the body of a mouse was irradiated with a dose of 1,500 r and at the end of definite intervals of time untreated tumor fragments were inoculated into the irradiated area. It was found that a high percentage of tumor transplants failed to grow if the implantation was done within two hours after irradiation, while those which did not dis-

appear in the irradiated area grew at a much slower rate than the controls. However, when untreated tumor tissues were implanted in the irradiated area seven days after irradiation, not only was the number of tumor takes greatly increased (almost 100 per cent), but the rate of tumor growth was almost normal.

This work is being continued and extended to include a study of the rate of recovery of tissues after irradiation, *i.e.*, recuperation of tissues from the damage caused by radiation as shown by their susceptibility to tumor transplants.

SUMMARY

1. The effect of 200 kv. roentgen rays on Mouse Sarcoma 180 in animals has been studied. Tumors, 0.3 to 1.5 cm. in diameter, were irradiated *in vivo* through a hole slightly larger than the cross-section of the tumor in a lead shield 5 mm. thick.

2. No tumor regressed with a dose of less than 500 roentgens, and very few with less than 750 roentgens. With a dose of 1,000 roentgens, about half of the cases showed complete regression, but with a dose greater than 1,500 roentgens, tumor regression occurred in almost 100 per cent of cases.

3. The radiosensitivity of Mouse Sarcoma 180 *in vitro* and *in vivo* has been compared. It was found that the lethal dose for the tumor growing in the animal was found to be about half of the dose required to destroy the viability of the same tumor *in vitro*.

I wish to express my thanks to Dr. G. Failla for his co-operation and valuable suggestions during the course of the present study.

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ROENTGEN-RAY EVIDENCE OF METASTATIC MALIGNANCY IN BONE[1]

By HENRY SNURE, M.D., *and* GEORGE D. MANER, M.D., *Los Angeles*

SEVERAL years ago, following an autopsy on an extremely emaciated individual, we reviewed the roentgenograms of his lumbar spine, which had indicated changes in the fifth lumbar body alone. Autopsy showed macroscopic evidence of metastatic malignancy throughout most of the vertebral bodies. Microscopic examination proved that tumor cells had replaced most of the marrow cells without destroying the trabeculæ of the spongiosa; however, there were several areas about one centimeter in diameter where the trabeculæ were destroyed that could not be demonstrated on the film, and for this reason the present study was undertaken. Following this observation

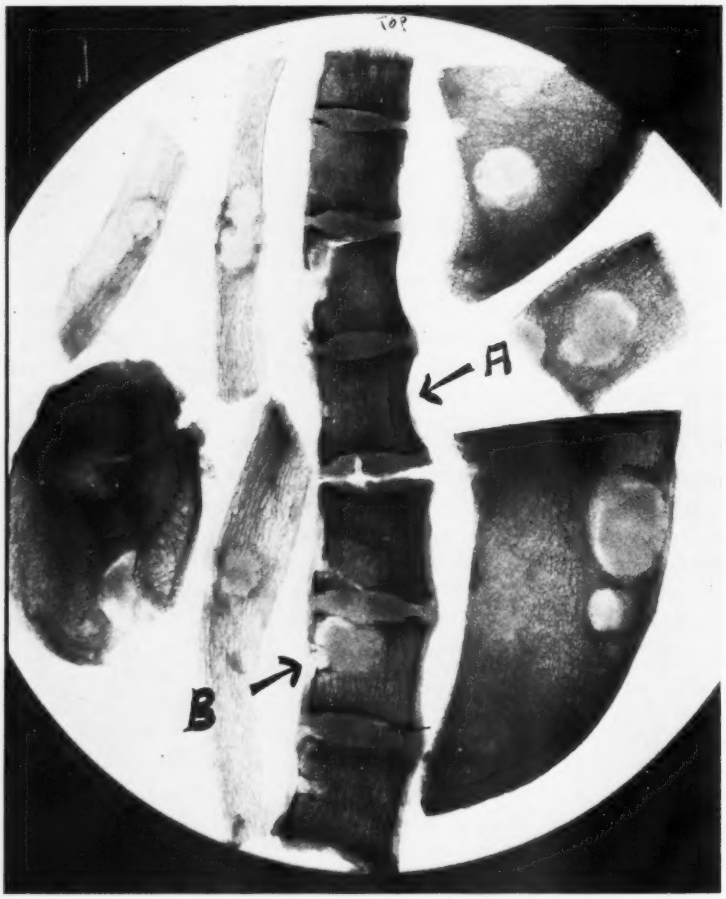

Fig. 1. Metastasis from primary carcinoma of the liver to the vertebræ, ribs, and ilii. Thin wedge of vertebra 0.5 centimeter in thickness removed by hammer and knife method is pictured in central portion of film. Vertebra marked *A* has as large a metastatic nodule as vertebra marked *B* but without roentgen-ray evidence of same. Compare density of cortical shadows with density of spongious portion.

[1] Presented before the Radiological Society of North America at the Twenty-second Annual Meeting, at Cincinnati, Nov. 30–Dec. 4, 1936.

Fig. 2. Practically all of spongious bone has been removed from vertebra *A* and cavity filled with paraffin. No roentgen-ray evidence of same.

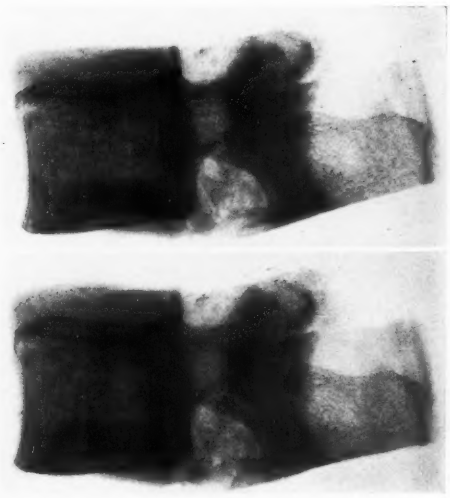

Fig. 3. Upper figure shows an area of cortical bone one centimeter square removed from one lateral wall of vertebral body. Lower figure, after filling space with paraffin, still shows changes present on roentgenogram indicating that cortical bone is responsible for most of detail depicted on the film.

we removed a V-shaped section of bone from the vertebral bodies of all patients dying of malignancy when autopsy was permitted. To avoid distortion due to the spine-film distance or to the superimposed shadows, we sawed the spinal column lengthwise in the sagittal plane and placed one-half directly on the film holder; even under these conditions the larger areas of destruction were not demonstrable on the film.

It is surprising how frequently metastatic malignancy is present in the vertebræ without clinical signs and without evidence on roentgenograms that have excellent detail and quality.

By merely taking a wedge of bone about one-half centimeter in thickness from the lumbar vertebræ we found several cases of metastatic malignancy originating from primary carcinoma of the liver, tongue, stomach, gall bladder, urinary bladder, pancreas, rectum, and other organs supposed to metastasize but rarely to the osseous structures. The largest number of metastases to the vertebræ was secondary to breast and prostatic carcinoma. The best method of study would be that suggested by Fraenkel, in 1899, of sectioning and roentgenographing all bones of the body. The fact that Fraenkel (1) found eight instances of metastasis to the vertebræ in the first 39 cases of gastric carcinoma he studied, indicates the correctness of his suggestion. Time, finances, and permission to do a complete autopsy prevents many of us from adopting Fraenkel's method. However, by using a heavy butcher knife and a hammer, a wedge of bone can be easily and quickly removed from the anterior portion of the vertebral column, and with little mutilation of the corpse. The lumbar area is the most frequent site of metastasis to the vertebræ, and the one from which the wedge of bone can most easily be removed. Distortion as a complicating factor is avoided by placing the thin wedge of bone directly on the film holder.

To determine the size of an area of metastasis that could be visualized on the

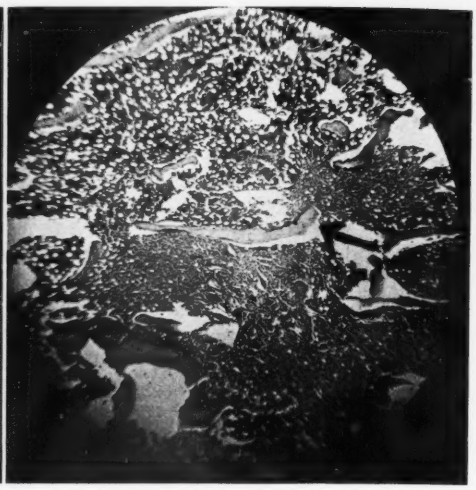

Fig. 4. Fig. 5.

Fig. 4. Photomicrograph of vertebral body showing a few isolated nests of tumor cells indicated by arrows. X are small trabeculæ. There is no roentgen-ray or macroscopic evidence of metastasis. Primary tumor was carcinoma of the breast.

Fig. 5. Photomicrograph of metastasis to vertebral body. Primary tumor of the urinary bladder. Arrow indicates trabeculæ unaltered, with normal marrow tissue above and masses of tumor cells below the same. Roentgen-ray evidence of this replacement type of metastasis cannot be demonstrated on the film.

roentgen film, we began by removing portions of the spongiosa of the vertebral bodies and filling the cavity with muscle scraps, water, or paraffin. Spongiosa occupying an area of 2 × 2.5 × 2.75 cm. and 1 cm. deep can be removed from a vertebral body, and roentgenograms, made after filling this space with paraffin, give practically no evidence of change in the spongiosa. It would be impossible to visualize on the roentgenogram an osteolytic tumor of the above size in the vertebræ of a living person in which fine detail of the spongiosa would be partially obliterated by the film-vertebral distance and by superimposed soft tissue shadows. Apparently the cortical bone accounts for most of the *detail* of the osseous structures depicted on the film, while the spongiosa accounts for the general density. When areas of cortical bone one centimeter square are removed from the lateral surface of the vertebral body and the excavated area filled with paraffin, their location can be seen on the roentgenograms. Holes, made by a trephine one centimeter in diameter and extending almost across the vertebral body after filling with paraffin, are not visible unless the central ray passes through the long axis of the hole and are not visible then if the cortex is replaced. In the anteroposterior view, on the film, you will find the superimposed parts of the posterior arch practically obscuring all evidence of holes when filled with air only. However, when filled with paraffin such holes are not visible on the film.

Similar findings can be demonstrated in other bones of the body. Films made of the tibia, with spongiosa of the marrow cavity (two centimeters in diameter) removed and filled with paraffin, show no change when compared to films of tibia before removing spongiosa, the soft tissues (such as muscle) remaining in place in both instances. Likewise, an os calcis can be sawed lengthwise into halves, spongiosa curetted out, and a space from one and one-half to two centimeters in diameter filled with paraffin, there resulting no evidence of change on the subsequent film. Ribs sawed lengthwise and marrow curetted out show no deviation on the film from the normal. In the case of the ribs

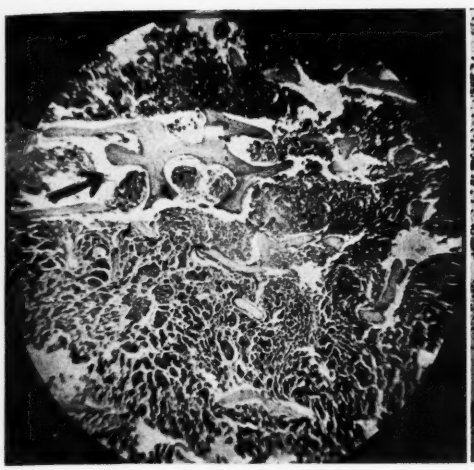

Fig. 6.

Fig. 7.

Fig. 6. Photomicrograph of replacement type of metastasis to vertebral body; primary tumor is carcinoma of the stomach. Arrow points to minor trabeculæ that are unchanged. Normal marrow above trabeculæ with masses of tumor cells below; there is a tendency to gland formation in some areas.

Fig. 7. Photomicrograph of metastasis to vertebral body—primary carcinoma of the breast. Tumor cells are scattered throughout marrow tissue. Trabeculæ much enlarged; note osteoblasts along borders of the trabeculæ as indicated by arrows. This is the osteoplastic type of metastasis which usually does give roentgen-ray evidence of its presence.

no paraffin was used and it was not necessary that the halves of the ribs fit accurately upon each other.

A demineralization of all vertebræ, ribs, and pelvic bones was the only roentgenographic evidence of metastasis in two cases of myeloma in which we had made roentgenograms. Fraenkel also reports two similar cases of myeloma, but in each instance he had lateral views of the chest which showed an S-shaped deformity of the sternum. He says this does not occur in other types of metastasis. Simpson (2) reports a case of prostatic metastasis to nearly all the vertebræ, with only microscopic evidence of its presence. No change could be detected macroscopically when the vertebræ were sawed in two. This type of metastasis might be referred to as the replacement type. It should be kept in mind that pains along the spine often referred down the legs may be the first signs of metastatic malignancy. A negative roentgenogram at this time should be disregarded, particularly if a primary malignancy is known to exist elsewhere in the body. Chemical tests for blood serum, calcium, inorganic phosphorus and phosphatase activity, as suggested by Gutman (3) *et al.*, are indicated as additional aids in the diagnosis of bone disease.

In studying the density of the epiphyseal plates, attempts were made to produce evidence of ruptured nucleus pulposus. With half of the fibrous intervertebral disc cut off the upper surface of a vertebra, circular and irregular shaped areas about one and one-half centimeters in diameter were depressed by tapping on small wooden or steel bars; variations of the spongiosa were barely visible on the film. A rubber-tipped metal cylinder one and one-half centimeters in diameter was driven through half of the fibrous disc, the epiphyseal plate, and into the body of the vertebra to various depths. When the holes were filled with paraffin, changes in the spongiosa were almost impossible to detect. The dense crescentic shadow usually found on films that visualize ruptured nucleus pulposus is probably due to a slow rebuilding of new bone at the rupture site rather than a piling up of the small fragments of the trabeculæ of the spongiosa displaced by the cartilage. It seems reasonable to assume that in a recent rupture of the nucleus

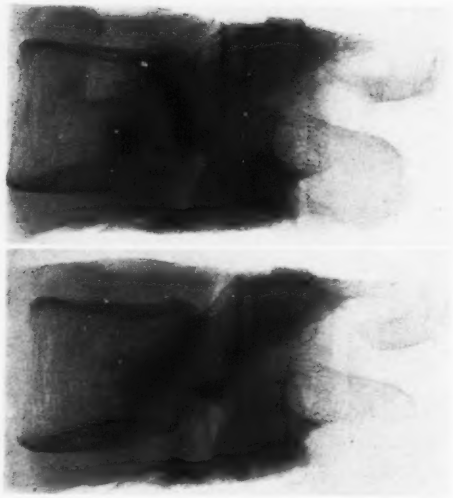

Fig. 8. Upper figure shows an air-filled nucleus pulposus rupture produced by rubber-tipped rod. Lower figure shows same with space filled with paraffin; no roentgen-ray evidence of same, indicating that *recent* ruptures of the nucleus pulposus give no roentgen signs.

pulposus no x-ray evidence of rupture can be demonstrated on the film.

The excellent experiments of Lachmann and Whelan (4) show that only under very favorable circumstances can a decalcification under 20 per cent be diagnosed, and in most bones a loss of from 20 to 40 per cent of calcium is necessary. In their experiment to determine the relative part played by the cortex and spongious layer in producing the roentgenogram, they found that in the vertebræ and os calcis the spongious portion was the most important for the production of density. In other bones the two bony structures shared about equally in the production of shadows. Variations were also found in different parts of the same bone.

It should be remembered that their experiments were made on the isolated bone and compared to a film of its normal appearance with no soft tissue shadows intervening. They also point out that decalcification by a biologic process may be different than that produced by chemicals. Slight motion of the living patient during the exposure of films must also be considered as a confusing factor.

No extensive comparison was made to determine relation between type of primary tumor and type of metastasis, but our observations lead us to believe that the theories given by Hastings and Downs (5) are correct. The tumors with considerable fibroblastic change usually give rise to the osteoplastic type of metastasis, and are, therefore, visible on the roentgenogram. Shields and Whitham (6) state that insofar as grading of tumors is concerned there is little evidence of correlation between the histologic appearance and extent of metastasis in the individual case, except that tumors, with many abnormal mitotic figures usually kill promptly and have widespread metastasis. Unfortunately, the metastasis may be the first sign of the disease, and may be preceded by a period of pain along the spine and referred down the legs with no roentgenographic evidence of the metastasis present.

After nearly completing our experiments we found that somewhat similar work had been done in 1928 by Chasin (7) in the study of two cases of proved tuberculosis of the spine. He reported one patient, 28 years of age, who did not give roentgenographic evidence of disease until one year after the onset; another patient, six years of age, presented roentgenographic evidence three months after clinical signs of tuberculosis were first noted. Later we also found the article by Böhmig and Prevöt (8) regarding the experimental production of ruptured nucleus pulposus. Our results in depicting on the film the artificially produced rupture of the nucleus pulposus did not agree with Prevöt's findings. In 37 per cent of Prevöt's proved autopsy cases no roentgenographic signs of ruptured nucleus pulposus were demonstrated. However, most of these were rather small in size.

GENERAL COMMENTS

(1) Widespread metastasis of malignant tumors to the osseous structures without demonstrable evidence in the roentgenograms is not an infrequent occurrence.

(2) A rapid and easy method of remov-

ing a wedge of bone from the vertebræ is suggested, recognizing of coruse, that complete removal of the spine and several sections of same is a superior method.

(3) By sectioning all bones at autopsy, Kaufmann (9) found 72 per cent of bone metastasis in prostatic carcinoma. Bumpus (10), by using the roentgenogram alone, found 30 per cent of prostatic metastasis.

(4) It is reasonable to suppose that destructive changes in the marrow space due to infection may likewise not be visible on the film.

(5) Distortion of detail on the roentgenogram is avoided by using a thin wedge of bone; this also requires less laboratory space.

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THE INTRAVENOUS AND INTRADUODENAL ADMINISTRATION OF RADIO-SODIUM[1]

By JOSEPH G. HAMILTON, M.D., *and* ROBERT S. STONE, M.D., *San Francisco*

From the Divisions of Medicine and Roentgenology, University of California Medical School

THE internal use of the radio-active elements was reported by many investigators in this country and abroad within a few years after these substances became available for medical purposes.

In 1914, Proescher (1) gave from 50 μgm. to 350 μgm. of radium chloride[2] by vein to more than a score of patients and stated that there were no immediate toxic manifestations to be noted. He stated that marked symptomatic and clinical improvement was observed in patients with arthritis and hypertension. Similar studies were made and conclusions reached by Field (2), Delano (3), Moriarta (4) and Pinch (5). However, these investigators did not make control studies, and their follow-up reports were inadequate.

Proescher and Almquist (6) reported the effect of radium given parenterally to a small series of rats and mice. They attempted to evaluate the relation between the amount given and the length of life after injection. They followed the blood counts of all the animals and noted the pathologic changes at the time of death. Death occurred in both rats and mice from 30 to 45 days after the administration of 900 μgm. to 1,300 μgm. of radium chloride per kg. of body weight.

Several mice received from 2,000 μgm. to 4,000 μgm. per kg. and died within a period of from seven to ten days. In these animals they found a transient rise of the erythrocyte and leukocyte counts, and a rapid and profound leukopenia with complete destruction of the polymorphonuclear forms. Central necrosis of the liver was noted in almost all of the animals. The lymph nodes and spleen showed degenerative changes with marked destruction of lymphocytes and numerous small areas of necrosis. In the bone marrow similar changes were seen, accompanied by decrease of myeloid cells and rupture of the capillary walls.

Cameron (7) examined the organs of a woman who had received 1,000 μgm. of radium chloride by vein three and a half months prior to her death from a carcinoma of the uterus. He found from 0.006 μgm. to 0.0048 μgm. per gm. (dry weight) in the bone marrow, 0.0061 μgm. per gm. in the liver and smaller amounts in the other tissues. There were apparently no activity-measurements made of the bones.

Proescher and Almquist (8) described two patients who received large doses of radium over a period of many months. The first, a case of pernicious anemia, was given a total of 900 μmg. in nine months, and underwent a definite clinical remission which persisted up to the conclusion of the treatment. No subsequent report was made of the final outcome or of the patient's course after the therapy was discontinued. The second patient, a case of myelogenous leukemia, received 2,700 μmg. over a period of 17 months without any significant change in the erythrocyte or leukocyte counts. Arneth (9) treated a patient with pernicious anemia with a stated total of 380 E.S.U. of thorium-X over a period of four months, and at the end of that time noted a marked remission associated with an increase of the leukocyte counts. Hirschfeld and Meidner (10) conducted an extensive study of the effect of the intravenous

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[1] Presented before the Radiological Society of North America at the Twenty-second Annual Meeting, at Cincinnati, Nov. 30–Dec. 4, 1936.

[2] All quantities given are expressed in terms of radium element.

administration of thorium-X upon a large series of mice, rats, rabbits, and dogs. They found the comparable lethal doses, expressed as radium equivalents, to be much smaller than those which Proescher and Almquist (6) reported using radium chloride. Stevens (11) treated six patients having different types of lymphomas, with x-ray and injections of radium. Each patient received from 150 μgm. to 250 μgm. of radium chloride by vein. Improvement was noted in four of the six patients, but, since x-ray therapy was given to all but one, no definite clinical evaluation of the effect of the radium could be made.

Seil, Viol, and Gordon (12) measured quantitatively the excretion of radium following the intravenous administration of 100 μgm. of radium chloride to a 23-year-old male. They found that over 40 per cent of the amount given was excreted in the feces, and only 2 per cent was eliminated by the kidneys. On the ninth day after the injection, no radium could be detected in the urine, and less than 0.5 per cent was excreted in the feces. Two months later the experiment was repeated upon the same subject and similar values were obtained. Seil, on two different occasions, took 50 μgm. of radium chloride by mouth; similar activity-studies were made and it was observed that within four days approximately 60 per cent was lost in the feces, but less than 0.15 per cent was eliminated in the urine during the first two days following the ingestion of the radium. During the last experiment it was found that, ten hours after the radium was taken, 588 μμgm. per liter was present in the expired air from the lungs, but at the end of 38 hours this amount had fallen to 70 μμgm. per liter. The authors came to the conclusion that soluble radium salts are eliminated principally by way of the intestinal tract, and that within a few days the radium becomes firmly fixed in the body tissues.

Barker and Schlundt (13) examined 10 patients who had received from 80 μgm. to 1,455 μgm. of radium chloride, and observed that relatively small amounts were retained. Schlundt, Nerancy, and Morris (14) measured the activity of a group of 12 inmates of the Elgin State Hospital who, altogether, had received a total of 2,190 μgm. of radium. At the end of six months, only 4.3 per cent was retained by these patients, and six months later only 1.9 per cent remained of the amount originally given. Schlundt and Failla (15) determined the rate of excretion of two women who had become radioactive twelve years previously. The activity of the first patient was found to be 24 μgm., and that of the second was 14 μgm. The coefficients of excretion per day were 0.005 per cent and 0.0026 per cent, respectively, and it was noted that over 85 per cent of the radium eliminated was present in the feces. They repeated the experiment of Seil, Viol, and Gordon (12) by taking from 2 μgm. to 5 μgm. of radium bromide by mouth, but observed that from 91 to 98 per cent was eliminated within from four to five days.

In 1925, Martland, Conlon, and Knef (16) described a group of cases of occupational poisoning in girls employed as dial painters in a watch factory. Later Martland (17) published a more detailed report concerning these unfortunate women. He discussed the relation between the cause of death and activity of the body at the time of death. The earlier deaths resulted from a profound anemia which was frequently complicated by necrosis of the jaw, and the activity of these patients was found to be as great as 180 μgm. The majority of the patients succumbing at a later date died from a rapidly growing type of osteogenic sarcoma. The members of the latter group were, on the whole, less radio-active, and one patient had only 10 μgm. contained within her body at the time of death. Several of the patients had developed bone changes suggestive of early sarcoma at the time the article was written. Flinn (18) examined a number of similar patients, and noted the same relation between the degree of activity of the patients and the cause of death. He described several living patients suffering from re-

peated pathologic fractures of the long bones and loosening of the teeth in whom the activity was as low as 2 μgm.

Gettler (19) reported the case of a man who consumed a total of 1,400 bottles of radium chloride, each containing 2 μgm., over a period of five years. The patient entered the hospital in a state of marked anemia and emaciation, which was complicated by an extensive necrosis of the jaw. Postmortem studies showed hyperplastic changes in the bone marrow. The activity of the entire body was found to be 73.6 μgm., with all but 0.5 per cent contained in the bones.

The inconclusive clinical results of the earlier work concerned with the internal use of radium, together with later reports of radium poisoning, have apparently served to discourage further investigation in this direction. The amount which would be sufficient to be clinically effective probably would be fatal within a few years, due to the tendency of the radio-active elements to be deposited in the bones.

In 1934, Curie and Joliot (20) announced that they had prepared a radio-active isotope of nitrogen by the bombardment of boron with the alpha particles of polonium. They were able to prove the chemical identity of the radionitrogen, and shortly afterwards radiosilicon and radiophosphorus were similarly obtained from magnesium and aluminum.

Lawrence and Livingston (21) designed and constructed a magnetic resonance accelerator with which they studied the effect of bombardment of numerous substances, using at first protons and alpha particles, and later deuterons. Soon after the discovery of radio-activity was announced, Henderson, Livingston, and Lawrence (22) reported that they had induced artificial radio-activity in the elements of the first two rows of the periodic table, using the cyclotron.[3] Later, Lawrence and Livingston (23) were able to stimulate radio-activity in elements as heavy as platinum. During the earlier phases of this work, the deuteron beam of the cyclotron carried an energy of a few microamperes at a potential of approximately 2 million volts (MV.). However, at the time of writing this paper, Lawrence (24) informs us that he and his co-workers have recently obtained an intense deuteron beam of over 100 microamperes at 6 million volts (MV.). With such an energetic beam it is possible to obtain as much as 1 gm. radium equivalent of radio-sodium.

In Figure 1 is shown schematically the nuclear reaction by which radio-sodium is formed. The rapidly moving deuteron, upon approaching the sodium nucleus (Na^{23}), becomes distorted in such a manner that the neutron is separated from the proton, the neutron entering the nucleus while the proton is repelled from the intensely positive field. When the Na^{23} acquires the neutron from the deuteron, it becomes heavier by the weight of the neutron and becomes Na^{24}. This isotope of sodium does not occur in Nature and is energetically unstable, and in the course of 14.8 hours, on the average, emits a high-speed electron from its nucleus. When this electron is discharged, Mg^{24} is formed, and the magnesium nucleus is left with an excess energy which is immediately radiated as a gamma ray.

The electrons (*i.e.*, beta rays) are emitted over a relatively broad spectrum, and, according to Kurie, Richardson, and Paxton (25), with an average energy of approximately 500 kv. Richardson and Kurie (26) state that the gamma-ray spectrum is composed of radiations carrying the energies of 1 MV., 2 MV., and 3 MV., with a ratio of intensity equivalent to 3:3:2.

In the Spring of 1936 the Radiation Laboratory of the University of California was able to furnish radio-sodium upon several occasions in amounts sufficient for clinical investigation. It was felt that many of the disadvantages of internal radium therapy could be avoided by the use of radio-sodium, inasmuch as this latter substance does not become fixed in the body tissues and the duration of its effect

[3] For the sake of brevity, the magnetic resonance accelerator is commonly spoken of as the cyclotron.

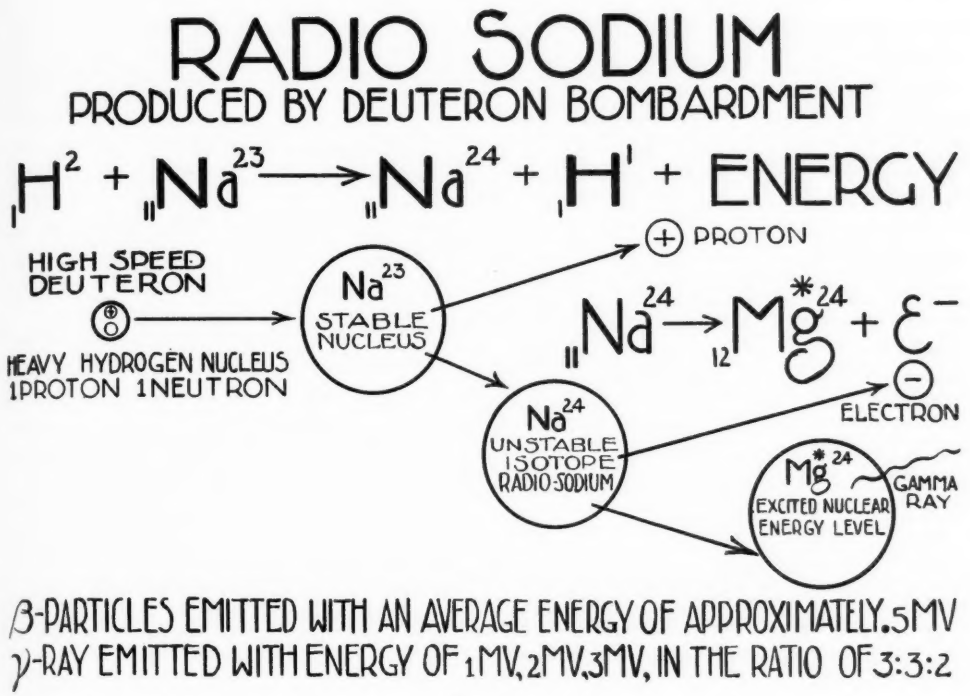
RADIO SODIUM
PRODUCED BY DEUTERON BOMBARDMENT
$_1H^2 + {}_{11}Na^{23} \rightarrow {}_{11}Na^{24} + {}_1H^1 + ENERGY$
HIGH SPEED DEUTERON
HEAVY HYDROGEN NUCLEUS 1PROTON 1NEUTRON
Na^{23} STABLE NUCLEUS
PROTON
$_{11}Na^{24} \rightarrow {}_{12}Mg^{*24} + \varepsilon^-$
ELECTRON
Na^{24} UNSTABLE ISOTOPE RADIO-SODIUM
Mg^{*24} EXCITED NUCLEAR ENERGY LEVEL
GAMMA RAY
β-PARTICLES EMITTED WITH AN AVERAGE ENERGY OF APPROXIMATELY.5MV
γ-RAY EMITTED WITH ENERGY OF 1MV, 2MV, 3MV, IN THE RATIO OF 3:3:2

Fig. 1.

is limited by the short half-life of only 14.8 hours. The patients whose protocols are given below were selected because they were the only individuals with leukemia available at such times as the radio-sodium could be obtained.

PREPARATION AND ADMINISTRATION OF RADIO-SODIUM

The samples given to the first patient were prepared each time by the deuteron bombardment of from 3 to 4 gm. of sodium chloride. The activated salt was brought quickly to the hospital, and dissolved in sufficient water to make an approximately isotonic solution which was filtered and boiled. The activity was measured with a small quartz fiber electroscope, and the solution immediately administered by vein to the patient.

The radio-sodium for the second patient was obtained each time by the deuteron bombardment of approximately 1 gm. of metallic sodium. This was dissolved in dilute hydrochloric acid of such a concentration (.147N) that when the solution became neutral to litmus, it was isotonic. The first dose was given by vein, but the second was introduced intraduodenally. This latter procedure was accomplished by passing a small Rehfuss tube under the fluoroscope so as to insure that the tip was well within the duodenum.

TECHNIC OF ACTIVITY MEASUREMENTS

A large Curie type of electroscope was used for the activity determinations of the last two samples, as well as for all the measurements of the radio-activity of the two patients and their body fluids. The instrument was calibrated against a 10.12 mg. sample of radium which had been previously checked by the United States Bureau of Standards. The radium standard was placed at distances of 160, 40, 20, and 15 cm. from the center of the chamber

of the electroscope. The varying rates of fall of the leaf over each portion of the scale were observed, so that the rate of discharge at any point upon the scale was known for each distance. The background was determined daily during the time that the instrument was being used, and the necessary corrections made. The units of measurement of activity are expressed as either millicurie equivalents (mc.e.) or microcurie equivalents (μc.e.).

The activity of each patient was determined by placing the electroscope at a distance of 160 cm. from the tip of the xyphoid process of the patient's sternum. The subject was always in the recumbent position with the knees drawn up and the arms folded across the chest. The difference observed in each experiment between the activity of the sample administered to the patient and the measured activity of his body immediately after injection, is considered to be due to the absorption of the gamma radiation by his tissues. The activities of the body fluids and feces were measured with the electroscope at a distance of either 20 or 40 cm., depending upon the strength of the sample. Several specimens were so feebly radio-active that determinations had to be made at a distance of 15 centimeters. Whenever possible, measurements of a given sample were made at two different distances. The activity of the sweat was obtained by measuring the activity of the bed-linen, night-clothes, towels, and the mattress, after the patient had been sponged and removed to another part of the building. The relative activities of the blood plasma and the corpuscles were obtained by centrifuging 50 c.c. of oxalated blood, washing the cells once with 50 c.c. of normal salt solution, and measuring the activity of the cells and then that of the plasma combined with the wash-fluid.

All the values given for the body-fluids were corrected for the amount of radio-sodium lost by decay during the interval of time between the collection and measurement of the samples.

REPORT OF CASES

Case 1. G. M., a white male, aged 29 years, entered the University Hospital in March, 1936. He had first noticed generalized adenopathy in February, 1935, and in July of the same year began to experience increased fatiguability, dyspnea upon exertion, and progressive enlargement of the abdomen. He was seen in the Outpatient Department in September, 1935, and transferred to the hospital where, after routine blood studies and a biopsy of a cervical lymph node, a diagnosis of chronic lymphatic leukemia of the aleukemic type was made. He received an intensive course of deep x-ray therapy and, after considerable improvement, was discharged. Before his second entry into the hospital there had been a recurrence of the symptoms mentioned above, accompanied by marked loss of weight. Physical examination when he re-entered showed him to be a male 55 kg. in weight, chronically ill, with a moderate degree of generalized lymphadenopathy, marked hepatomegaly, and a blood-cell count of 3,600 leukocytes per c. mm., with 80 per cent lymphocytes, 45 per cent hemoglobin, and 2,170,000 erythrocytes. After consultation, it was decided to make this patient the recipient of the first intravenous administration of radio-sodium. On March 23, 1936, he was given 11 mc.e. of radio-sodium by vein, and four days later he received 13 mc.e. more in the same manner. During the two-weeks period following the administration of the radio-sodium, no significant alteration of the blood picture or clinical condition was observed. At no time was there any reaction noted which might have suggested a toxic reaction to this substance. It was felt then that adequate time had been allowed for the experiment and that the patient should be given a course of deep x-ray therapy. Following the x-ray treatment he improved slightly and was discharged.

Case 2. O. R., a white male, aged 23 years, entered the University Hospital for the first time in September, 1936, with a

diagnosis of chronic myelogenous leukemia. He stated that for four years he had observed a slow but progressive enlargement of his abdomen; three months before entry his condition became much worse, with malaise, rapid enlargement of his abdomen, diarrhea, nausea and vomiting, and repeated bouts of fever. Physical examination showed a young man 65 kg. in weight, chronically ill, with a markedly distended abdomen which was almost entirely occupied by the spleen. The leukocyte count was 700,000 per c.mm., with 40 per cent neutrophilic myelocytes; the hemoglobin was 56 per cent, and the erythrocytes 3,100,000. He received 15 mc.e. of radio-sodium by vein on Sept. 20, 1936, and 39 mc.e. intraduodenally on Sept. 25, 1936. During the period of administration of the radio-sodium and throughout the following week there was no significant change in the blood picture, and the patient's general course continued to be unfavorable. He was then given deep x-ray therapy to the spleen, which was followed by an excellent clinical response, and he was discharged two weeks later. The same lack of definite clinical response and absence of toxic effect were observed with this patient as were noted in the first case.

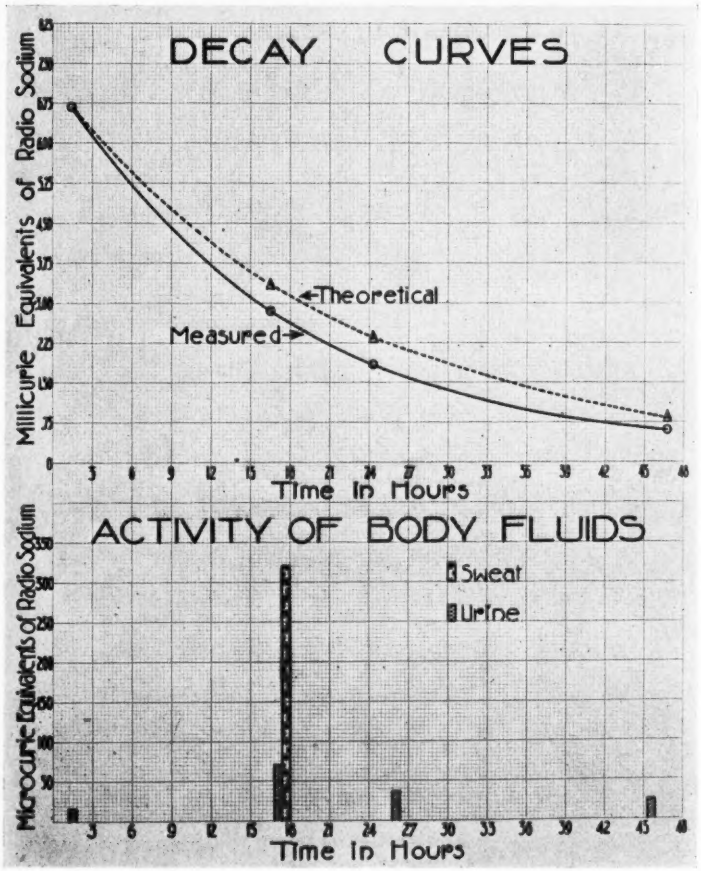

Fig. 2.

RESULTS

The lower curve (solid line) of the upper section of each chart (Figs. 2, 3, and 4) represents the actual measurement of the

patient's radio-activity following the injection of radio-sodium. The upper curve (dotted line) indicates the theoretical rate of decay of the radio-sodium. The lower portion of each chart illustrates the amount of activity observed in the various body fluids. The abscissa represents the intervals of time following injection, and the ordinate the degree of radio-activity.

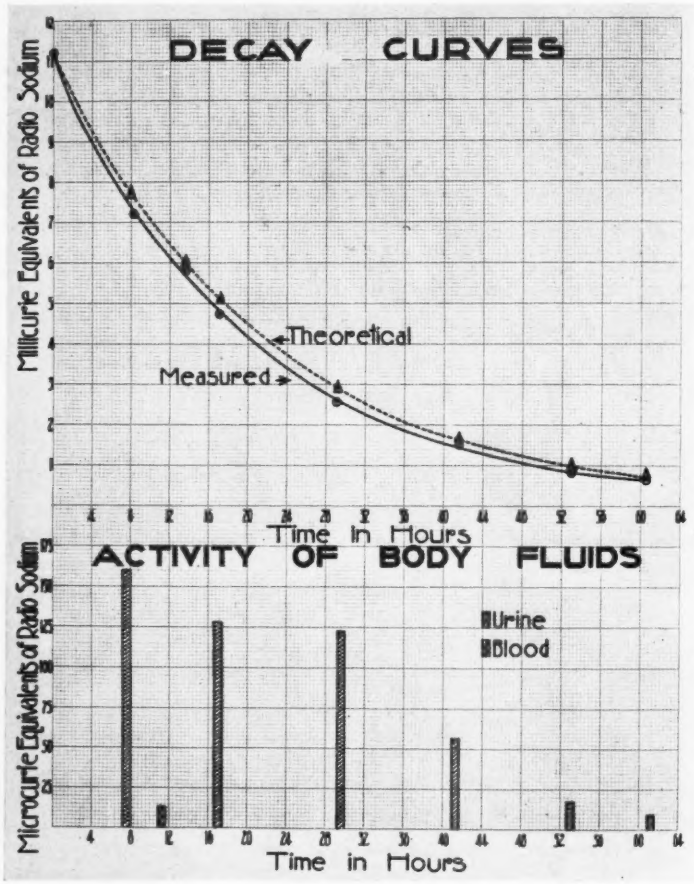

Fig. 3.

The values in Figure 2 were obtained following the administration of 13 mc.e. of radio-sodium to the first patient (G. M.). The initial measurement of the activity of his body was not made until one and a half hours after injection. The difference between the amount given and the first activity determination, allowing for the fact that in this instance the radio-sodium, prior to administration, was measured with another type of electroscope which was not available for accurate calibration.

The interval between the actual and the theoretical decay curves in Figure 2 is felt to represent the quantity of radio-sodium lost through the various channels of elimination. This view is borne out by the fact that the quantity excreted by the subject corresponds approximately to the difference between the two curves. The

large proportion of radio-sodium lost in the sweat can be explained by the fact that the patient had frequent and drenching sweats during his stay in the hospital.

In the third and final experiment, the second patient received 39 mc.e. by duodenal tube. A distortion of the first portion of the measured decay curve appears in Figure 4. In this instance, the radio-sodium at the completion of administration was concentrated in the duodenum and jejunum with the enormous spleen between the salt and the electroscope. Since it was felt that the absorption and distribution of the radio-sodium by the blood should have been complete within an hour, the theoretical decay curve was started at the second point of the measured decay curve. However, it is noted that the theoretical curve falls just below the actual curve and does not cross above the

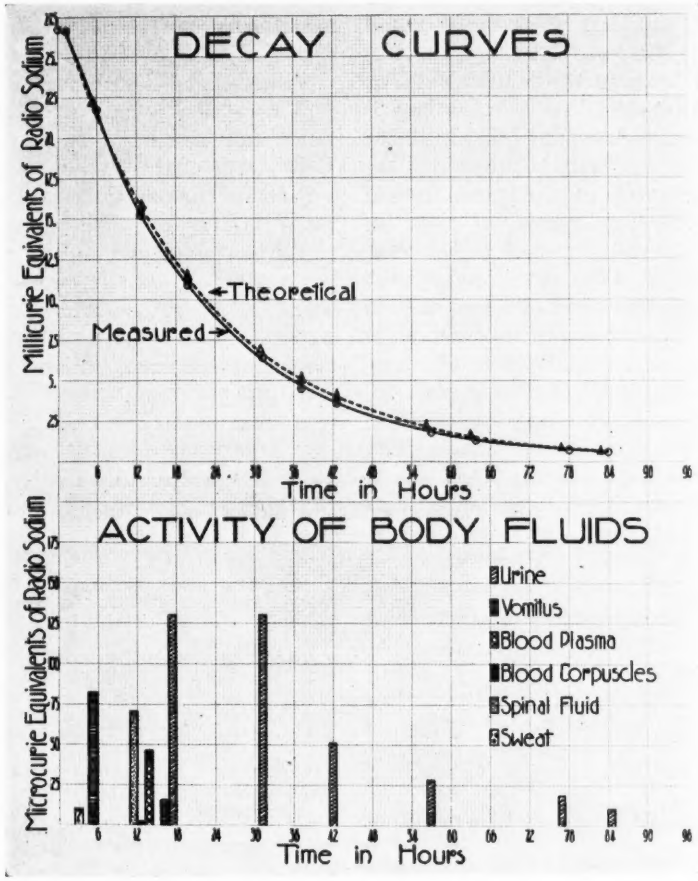

Fig. 4.

Following the administration of 15 mc.e. of radio-sodium to the second patient, it was observed (Fig. 3) that the amount lost in the urine was relatively greater than in the previous case, but no activity could be detected in the sweat, and the proportionate total loss was less. This result might be interpreted as being due to two factors: first, this subject received less sodium chloride; and second, he did not perspire as much. In addition, 100 c.c. of blood was withdrawn and its activity determined.

latter until more than six hours have elapsed; this observation suggests that absorption was not completed until more than six hours after administration of the radio-sodium. After equilibrium has been apparently established, it is to be noted that the gap between the two curves is relatively less than in the previous charts. Since the half-life of the radio-sodium is relatively short, the amount left within the body rapidly decreases. Similarly, the quantity eliminated over a given period becomes less as the interval of time increases from the moment of administration. Because of these two factors, the measured and theoretical decay curves approach each other toward the end of the period of measurable activity in all three experiments.

During this last investigation, the patient vomited twice, but no marked loss occurred from this source. Twelve c.c. of spinal fluid and 50 c.c. of blood were withdrawn, and their activities are expressed as μc.e. per 100 c.c. for the sake of comparison. The column for the blood is divided so as to represent the corpuscular and plasma activities. The value obtained for the sweat was only 1.2 μc.e. and cannot be clearly seen on the chart. The first urine sample was lost and is indicated as a question mark ("?"). In all three series of determinations, the activities of the feces were too feeble to be measured.

CONCLUSIONS AND SUMMARY

1. Radio-sodium can be given internally to human subjects without toxic effect, in amounts up to 53 mc.e.

2. The rate of decay within the body, the proportion eliminated, and the concentration of radio-sodium in the body fluids can be directly measured.

3. The quantity of radio-sodium given did not produce observable clinical effects. Further investigations with the use of larger amounts in other patients are essential before any estimation of its therapeutic value can be made.

4. Less than 10 per cent of the total amount of radio-sodium given was observed to have been eliminated by the body within the period of its measurable activity.

5. A new method has been developed for studying the metabolism of sodium within the body. A similar line of investigation can be followed, using other artificially prepared radio-active elements.

We are deeply indebted to Prof. Lawrence and his co-workers in the Radiation Laboratory of the University of California for their co-operation in preparing the radio-sodium and their advice concerning physical measurements; also, through them are we grateful for the support of the Research Corporation, the Chemical Foundation, and the Josiah Macy, Jr., Foundation, whose contributions made possible the supply of radio-sodium. We have been encouraged and advised by members of the Medical Department, and especially by Dr. S. R. Mettier and Dr. E. H. Falconer, to whom we express appreciation.

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DISCUSSION

DR. ROBERT R. NEWELL (San Francisco): I am much interested in the possibilities of radio-sodium given by vein. Radium by vein has proved disappointing and dangerous. I have not used it since seeing spontaneous fractures of both femoral necks after a total of about half a milligram of radium.

Dr. Stone gave a total of 50 "millicuries equivalent" of radio-sodium, a relatively enormous dose. But, of course, it decayed rapidly (seven times as fast as radon, even), leaving practically none after a week, whereas my patient's radium was incompletely excreted, some of it persisting (in the bones) for years. But there is more difference than merely a low intensity for a long time *versus* a high intensity for a short time. We are comparing the doses on a basis of "millicurie equivalents," which mean gamma-ray measurements. Now radio-sodium gives only hard gamma and beta, but radium (including its products) gives also alpha ray in tenfold total energy! So for intravenous therapy we ought to say that for *initial activity* one milligram of radium equals ten millicurie equivalents of radio-sodium.

But the absence of alpha radiation is precisely the thing that interests me most in radio-sodium. It means that the tissue ionization is similar by intravenous usage to what it is by external irradiation. Whereas for radium intravenously, the picture is dominated by the alpha rays with ionization one hundred times as dense along their tracks. I mean, there is physical basis for expecting a qualitatively different biologic action. (Professor Lawrence's paper, read later, on neutron rays has concern with this same difference.)[1] Clinical experiments with radio-sodium by vein ought to be carried further.

DR. STONE (closing): I want to add one thought in connection with this subject: We did not observe these patients as long as we should have liked to observe them. As any of you know who try anything new, when you have to deal with patients who belong to other clinicians—and in our hospital this condition applies to the clinic patients as well as the private—one has to produce results.

They all knew, and we knew, that giving x-ray treatments to these patients would improve their condition. Therefore, the experiments were continued only as long as we dared let the patients go and then x-ray therapy was given. The experiments terminated of necessity at that time.

We say there were no clinically observable effects. We know there were no clinically observable effects within the period of about two weeks of observation. We justify that short period of observation because, with x-ray therapy, you usually see observable clinical effects much before two weeks on patients of this type. However, we were particularly interested in

[1] Added by Dr. Newell later.

seeing what the reaction of these patients would be and the paper as published shows that the doses we gave were gradually increased. We intend to step the doses up to much larger amounts to see what will happen.

After all, we are only putting sodium chloride into the patients and there can be no toxicity, but that had to be proved before we could go to tremendous doses.

Dr. Newell mentioned the fact that there are no alpha radiations from radio-sodium. This may account for the lack of response to large doses—when patients respond to such small doses of radium chloride. One of the interesting features of artificially activated elements is that each has a slightly different type of radio-activity. This fact may be of therapeutic value in the future.

NOTE OF A NEW AND APPARENTLY USEFUL BIOLOGICAL INDICATOR OF X-RAY DOSAGE

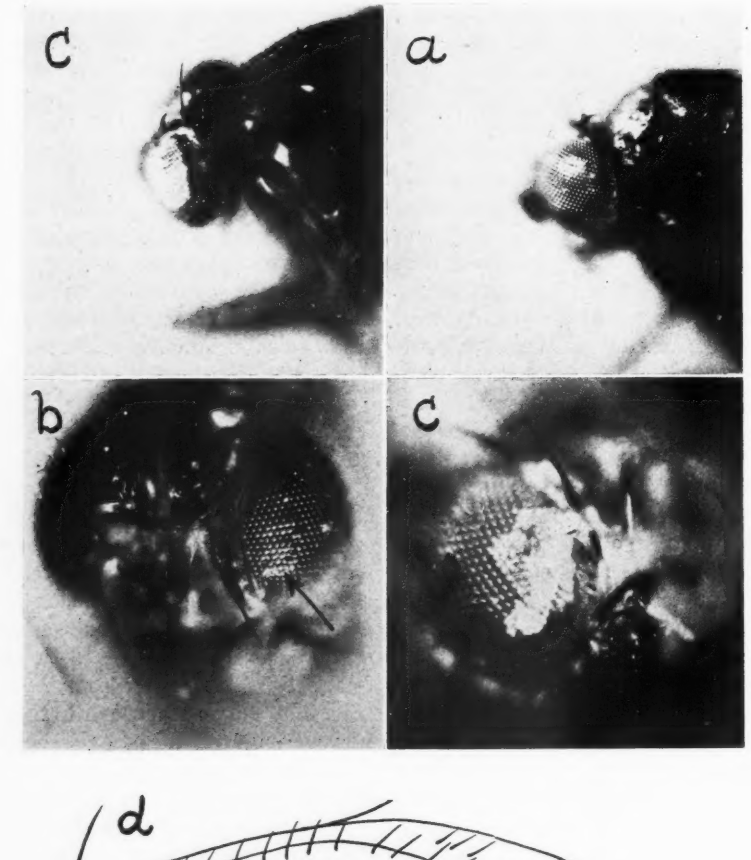
By C. P. HASKINS, PH.D., *Schenectady, N. Y., and* E. V. ENZMANN, PH.D., *Cambridge, Mass.*

From the Haskins Laboratory, Schenectady, N. Y., and Biological Laboratories, Harvard University, Cambridge, Mass.

IT HAS long been recognized that fundamental investigations of the physiological effects of electromagnetic radiations of high quantum energy are very largely dependent, on the biological side, upon the availability of suitable test objects. Such test objects should be small in volume but of such size as to be readily visible to the naked eye so as to minimize the technical difficulties involved in the examination of large numbers; should be available in such quantities as to be adaptable to long-range statistical investigations involving large populations; should be genetically and physiologically standardized to as great an extent as possible, and should, above all, present sharp and unmistakable end-points as criteria of effect.

A very considerable range of material has been explored in the past in an extensive effort to locate and standardize such a tool. Probably nothing has been found more generally adaptable and suitable for fundamental investigations in the biological effects of x-rays and cathode rays than the ova of the fruit fly, *Drosophila melanogaster*. The technic of rearing and handling the flies, isolating, raying, and observing the eggs has been extensively described by Packard (1), P.S. and C.T. Henshaw (2), Glocker and his collaborators (3), and others, and is well known. So far as is known to the authors, failure of the larva to emerge from the egg, or abnormalities of embryonic development have been the criteria of effectiveness used, and wild-type stock has been employed in every case.

For several years the writers have been engaged in a reasonably extensive statistical study of the incidence of mosaic colorless patches in the ommatidia of the compound eyes of adults of eosin *Drosophila melanogaster* x-rayed as eggs or very young larvæ, continuing an investigation initiated by Patterson (4), in 1929. A study was originally undertaken of the frequency distribution of mosaics of white eye color, resulting from somatically affected cells of the eye anlage, in an x-rayed population as a function of the incident energy input. The original purpose of the work was to so treat the data as to give information, first, of the number of ion passages required to traverse a given genic locus to achieve the desired effect, and second, the magnitude of the volume or aggregate of volumes in a cell within which the "hit" must occur. After considerable acquaintance with the material, however, the authors have come to feel that it presents a sufficient number of unusually desirable characteristics as a biological indicator of x-ray dosage to be possibly worthy of wider application in therapeutic work. The effect sought presents a sharp, reliable, and readily observed end-point, its frequency of occurrence varying with x-ray dosage at a single series of wave lengths in so direct a fashion as to indicate that a rather simple effect may be involved. It has been reproducible by different workers to within less than the probable error of any determination, and the populations required are not excessive, although definitely greater than in the case of killing experiments. Finally, the information derived is capable of use in a number of auxiliary investigations of possible interest, as will be described. It is with the hope that it may be of some possible interest or help to others interested in the field that a description of the material and its application is given.



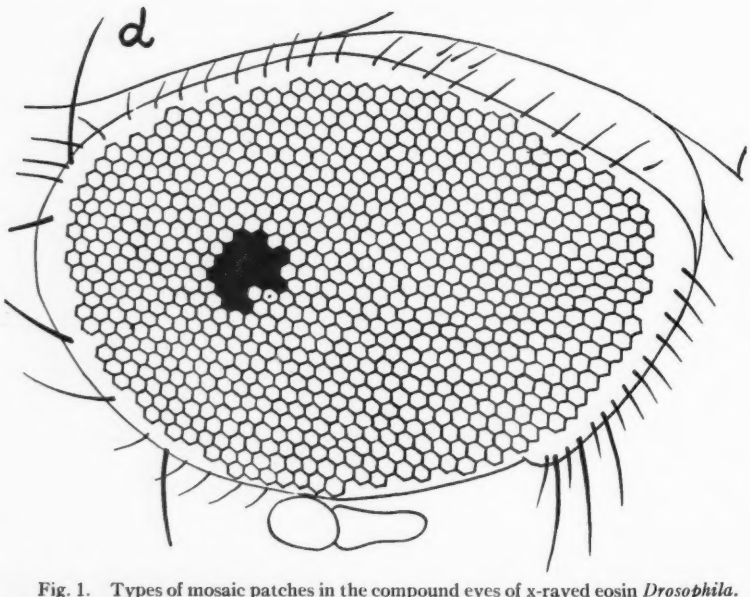


Fig. 1. Types of mosaic patches in the compound eyes of x-rayed eosin *Drosophila*. (*a*) Affected male, showing white patch on light eosin background. (*b*) Affected female, showing light eosin patches on dark eosin background. (*c*) "Double-white" female, showing white patch on dark eosin background. (*d*) Diagrammatic representation of typical patch in upper lobe of compound eye.

NATURE OF MATERIAL

Patterson has shown that x-rayed larvæ of *Drosophila* may at maturity bear mosaic patches of white eye color, composed of somatic tissue arising from single cells of the eye anlage affected at the time of irradiation. The anlage cell rather than the whole organism can thus be made the individual of experiment, and the number of mutations in irradiated material increased owing to the number of cells in the anlage at the time of treatment.

The stock of *Drosophila* selected for the present experiments was homozygous eosin. Two strains were used, one obtained from the Turtox Service Department, at Chicago, the other through the courtesy of Dr. G. Pincus, of this laboratory. The factor is genetically bicoloric. Mosaics in the males take the form of white, irregular patches composed of a variable number of ommatidia, superposed on the light eosin, male-color background. In the females, the observed patches, of the same shape and size range as in males, are composed of light eosin or male-color ommatidia superposed on the dark eosin, female-color background. Very rarely does a white patch occur against the dark eosin background. We have indicated elsewhere (5) that the observed frequency of occurrence of this condition corresponds rather closely to the expected frequency on the assumption that in such cases the given cell nucleus was inactivated at both white loci by separate electron passages. The characteristic appearance of mosaic patches in the male, female, and "double-white" female is shown in the accompanying figures. It is of interest to notice that Patterson has presented good evidence to show that these changes are in eosin stock entirely due to so-called "single-locus" mutations, since chromosome aberrations in the female take the form of dark-eosin patches, which are indistinguishable against the already dark-eosin background. In males, large chromosomal deletions result in the production of pits in the eye surface, since they seem to be fatal both to the cell involved and to the ommatidia which would have descended from it (Fig. 1, *a*, *b*, *c*, and *d*).

EXPERIMENTAL PROCEDURE

Flies were reared in half-pint milk bottles containing cooked banana-agar or corn-meal-molasses-agar medium, and inoculated in some cases with the standard brands "G-M" culture of yeast, in others with cells from standard commercial Fleischmann cakes. Slanting milk bottle cultures have been used in these laboratories for some time, and have proved much superior to the usual ones. In the latter, excess carbon dioxide is often trapped below the agar block, forcing it upward and submerging and destroying pupæ and adults, and limiting the available space upon which larvæ may feed. "Gassing" has been eliminated in the slant cultures, and the oblique surface provides a much greater feeding area, permitting a larger yield of flies per bottle. To ensure the obtaining of many cultures of uniform slope, and to permit the handling of bottles in quantity, one of us (E. V. E.) has devised the rack here figured, the dimensions being so chosen that it will hold 25 half-pint milk bottles, and will fit into an autoclave of standard size. Racks of this type have proved of great convenience, the bottles being held at an angle of 45° and most effectively used with about 50 c.c. of medium (Fig. 2).

It has been found of less importance in this work than in that of Packard and Henshaw that the ova used be of very nearly uniform age. However, an age spread from time of laying of more than six hours is not desirable. To prevent this situation, eggs were collected on drops of the agar medium mounted on glass plates, over which were inverted clean glass bottles containing a population of continuously laying adults. The plates were changed at intervals corresponding to the allowable age spread of the embryos. The use of young females from fresh cultures largely overcame the difficulties of egg retention, as indicated in Table 1-*A*, in

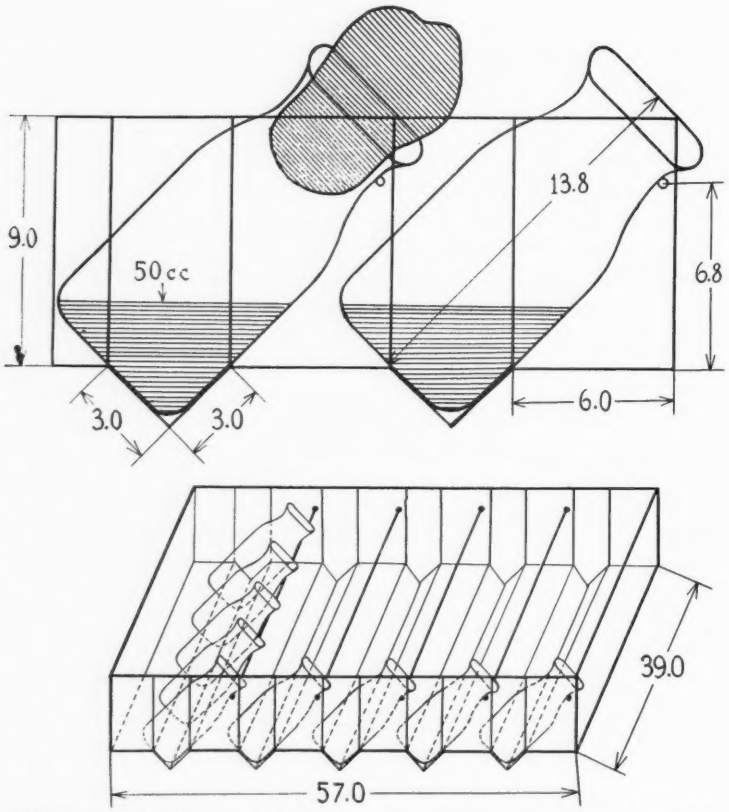


Fig. 2. Slanting bottle rack used with good success in rapidly making large numbers of slant cultures.

TABLE I.—SHOWING THE NUMBER OF LARVÆ HATCHED AT THREE-HOUR INTERVALS FROM A GIVEN NUMBER OF EGGS

Time from End of Egg-laying (hr.)	(a) No. Unhatched Ova	(a) No. Larvæ	Time from End of Egg-laying (hr.)	(b) No. Unhatched Eggs	(b) No. Larvæ	
0	132	0	0	1,130	0	
3	125	7	3	1,124	6	
6	123	2	6	1,123	1	
9	121	2	9	1,123	0	
12	121	0	12	1,122	1	
15	118	3	15	1,109	13	
18	110	8	18	914	195	Total
21	21	89	21	296	618	1,062
24	7	14	24	105	191	larvæ
27	0	11*	27	73	32	
			30	61	12	
			33	61	0†	

* Error of counting = 4 larvæ.

† Of the larvæ, 61 failed to hatch: the error in counting was seven eggs.

which are listed all larvæ hatching from a sample of 132 eggs laid at room temperature (22.5° C.) during an interval of one hour. The females were taken from a culture seven days old. It will be seen that a certain number of retained eggs were deposited which hatched between three and nine hours after deposition. The maximum of presumably freshly fertilized eggs hatched at 21 hours after deposition, the total spread of this class being between 15 and 24 hours. In Table 1-*B* is shown similar data for a larger population, the laying interval in this case being three hours, and the females having been derived from a two-day-old culture. The percentage of delayed eggs is low, but there is an increased variability in the hatching time of undelayed ova.

The agar drops were incubated at room temperature (22.5° C.) for 24 hours from the time of first exposure to the laying flies, when they were irradiated and immediately transferred to fresh culture bottles, where the larvæ developed. Conditions of back-scatter were kept constant in all experiments. The eyes of adult flies from irradiated eggs and larvæ were carefully examined for mosaic patches under a binocular stereoscopic microscope. Affected eyes were mounted in high-refractive media and studied further. Counts were independently checked in separate experiments by six workers, with good confirmation.

A single source of radiation was used, since the effect of dosage alone was studied in this work. It was a Coolidge x-ray tube of the "portable" type, air-cooled and with tungsten target, of lead glass with a sodium glass window. It was self-rectifying, and was operated directly from a line voltage of 125 v. through a transformer at a potential of 85 kvp. and a current of 10 ma. The distance from the outer surface of the sodium glass window to the upper surface of the irradiated material was kept constant throughout at five inches, the only variable being the time of exposure. The radiation was unfiltered except by the soft-glass window. Measurements of the energy incident at the point of exposure of the material were made with a Failla radium-compensated ionization chamber, using a collodion-graphite thimble in one case, and in the other with a calibrated Victoreen dosimeter. The output was found to be 78.1 roentgens per minute.

RESULTS

The following table, representing the combined data for all experiments, for males only, shows the total number of eyes counted for each x-ray exposure, the number in which whitened facets were discovered, the percentage of the total which these exceptional eyes constituted, and the percentage probable error of each determination. The percentage error was calculated for each exposure from the formula

$$\text{P. E.} = \pm 0.6745 \frac{p \times q}{n}$$

where n is the total number of eyes observed,

$$p = \frac{\text{number of affected eyes}}{n} \text{ and}$$

$$q = \frac{\text{number of unaffected eyes}}{n}$$

Exposure	Total Number*	Number Affected	Percentage Affected	Probable Error (Percentage)
Control	3,143	0	0.00	
1/4 min.	1,716	2	0.12	±0.057
1/2 min.	2,884	8	0.28	±0.075
1 min.	4,616	23	0.50	±0.070
2 min.	2,114	18	0.85	±0.135
3 min.	1,740	26	1.49	±0.195
4 min.	2,215	38	1.72	±0.185

* It will be noticed that the total number of eyes given is sometimes odd. This situation results from the method used in counting. To facilitate rapidity, one eye only of each fly was counted in many cases. This, because of the random distribution of modified patches in right and left eyes, is considered a justifiable procedure.

Below is shown a plot of percentage of affected eyes as a function of exposure time, the points determined being represented by the center crosses, and the lengths of the vertical lines indicating the probable error of each. It will be seen that a straight line may be considered

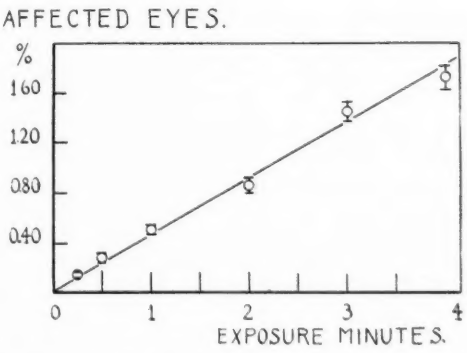


Fig. 3. Plot of percentage of affected eyes against dosage. Lengths of vertical lines indicate percentage of probable error in each determination.

the best fit for the seven points available (Fig. 3).

DISCUSSION

We have indicated elsewhere the significance which the linear curve may be thought to have in genetic investigations of the volume of loci of chromosomes. It is desired here to point out one or two features resulting from it which, it is believed, indicate good adaptability of the tool as a radiation indicator.

The linearity of the curve gives considerable evidence that the end-point used results from a relatively simple transition in cell nuclei, and is effected by a less complex series of interactions than is involved in the death of the organism. The end-point sought is sharply distinguishable by trained workers. "Borderline" cases, in which the observation of the effect becomes a matter of personal variability in the observer, are excessively rare if not absent. The effect, as already stated, has been found reproducible from stock to stock of eosin, and from observer to observer, within the limits of probable error given. Whether the effect will be reproducible from one allelomorph of eye color to another remains to be determined.

It is believed that the tool may prove quite adaptable in a study of the relative effectiveness of equivalent incident or absorbed dosages of different types of energy, as well as of the same type administered under differing conditions. Thus an investigation of a possible temperature coefficient for the reaction is in progress at the moment. A study of changes of slope or form of the curve for equivalent absorbed doses of x-rays of different quantum energies will be of interest. Such work is in progress, and is planned at four wave lengths. Locher (6) and others have indicated the importance of a study of the biological effect of neutrons, particularly because of the peculiar absorption characteristics of certain elements for them. Thus while, in the case of gamma radiation, the energy absorption of the organism is directly proportional to the number of electrons present per atom, hence approximately to the atomic number of the element, in the latter it is very largely due to hydrogen atoms. In such an investigation the tool described would seem to be of use, and, due to the courtesy of E. O. Lawrence, R. E. Zirkle, P. C. Abersoeld, and E. Dempster, work in this field has been begun. Similarly, the tool would seem to be equally adaptable to work with alpha particles, beta or gamma rays, or cathode rays.

The indicator has proved useful in connection with one or two investigations in the physiology of irradiated cells which may be mentioned in closing. Thus it is possible to derive considerable information of the relative rate of propagation of affected ("whitened") and unaffected cells from a study of the proportion of affected ommatidia in a given compound eye as a function of the number of cells in the eye anlage at the time of irradiation. Patterson, in the work already mentioned, has found that the size of mosaic spots produced varies with the age of the larva at the time of irradiation, the patches decreasing in number of elements with increasing age. We have been able to confirm this, and to further show, by direct cytological examination, that the number of cells present in the anlage at the time of irradiation corresponds rather closely to the quotient of the total number of ommatidia in the adult eye and the number affected, indicating that the rate of propagation of cells affected in the observed manner is unchanged relative to those not so affected. Thus averages of cell counts from the best sections of anlagen obtained, made perpendicular to the long axes of the elements, gave 15.6 as the mean best figure for the cell number in the primordia of larvæ between eighteen and twenty-four hours of age, reckoning from the time of laying. An average of counts of affected ommatidia in adult flies arising from larvæ irradiated at the same age, treated at exposures of one-half, one, two, three, and four minutes, involving a total of 31,734 facets, yields 12.7 as the best

figure, in reasonably close agreement. There is indication of little variability in sensitivity to x-rays for this effect as a function of age of the organism, from 18 hours onward, at least. Information of the preferred planes of division of affected cells can be obtained from a study of the shapes of mosaic patches under various conditions of irradiation. Data can likewise be obtained relative to the number of ion passages required to achieve the effect, the relation of spot size to dosage, sex, and portion of the anlage affected, as indicated elsewhere (Fig. 4).

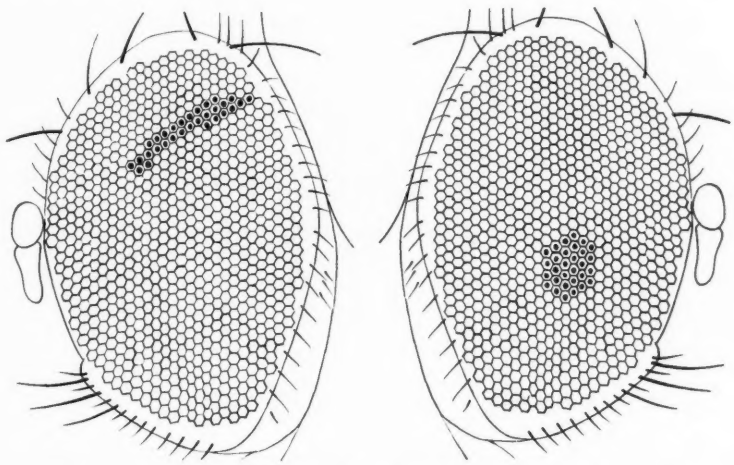


Fig. 4. Diagrammatic representation of mosaic patches of variant shapes.

All in all, it is believed that the induction of patches of mosaic eye color in stock of *Drosophila melanogaster*, originally described by Patterson, may well prove a useful indicator in studies of the biological effectiveness of x-rays and other forms of electromagnetic and particulate energy in biological material.

SUMMARY

A description is given of an effect of x-rays in producing mosaic patches of modified eye color in the compound eyes of imagoes of certain stocks of *Drosophila melanogaster* irradiated as eggs or young larvæ. The effect was originally described by Patterson and has been further investigated by the present authors. It is believed that it may well constitute a useful tool in investigations of the biological effect of x-rays upon small test objects, and reasons for this viewpoint are detailed.

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ROENTGEN KYMOGRAPHIC STUDIES OF CARDIAC CONDITIONS[1]

By WENDELL G. SCOTT, A.B., M.D., SHERWOOD MOORE, M.D., *and* HOWARD A. McCORDOCK, B.S., M.D., *St. Louis*

From the Edward Mallinckrodt Institute of Radiology and the Department of Pathology, Washington University School of Medicine, Saint Louis

ROENTGEN kymography is an objective and accurate method of recording the physiological movements of an organ or structure on a single x-ray film. The original idea was conceived by Bronislaw Sabat (1), in 1911, when he was a physiologist in Warsaw, Poland. The American pioneer in the development of this work was A. W. Crane (2), of Michigan, who, in 1915, presented his kymograph, elucidated the principles of kymography, and pointed out its application in the study of heart disease. In 1928, Pleikart Stumpf (3), of Munich (Fig. 1), made and later perfected a kymograph with multiple slits. By 1931 (4) he had developed the procedure so that it was practical and of clinical value. I. Seth Hirsch (5, 6) introduced multiple-slit kymography to this country in 1934, improved the technic, and made important clinical contributions. It was his work that stimulated our interest in kymography.

Fig. 1. Professor Pleikart Stumpf, a. o. Universitätsprofessor, Facharzt für Röntgen- und Lichtheilkunde, Munich, Germany. Dr. Stumpf originated multiple slit kymography and is to be credited, more than anyone else, with its subsequent development and application to the study of heart disease.

The procedure is simple (Fig. 2). The essential part of the apparatus is a large lead sheet in which narrow, horizontal slits are cut every 12 mm. apart. Each slit is 0.4 mm. in width, as advocated by Hirsch. This sheet is called the "grid." In our technic it is stationary. The film or cassette is placed behind the grid, and during a single, continuous exposure of about one and one-fourth second the x-ray film slowly moves down behind the grid a distance slightly less than the space between the slits, or actually 11 millimeters. This leaves 1 mm. of white, unexposed film which divides the kymogram into frames and prevents an overlapping of exposures. It must be clearly understood that it is the movements of only those areas on the border of the heart that overlie a slit which are recorded on the film as it moves down behind the grid. For a more detailed discussion of the apparatus[2] and discussion of the principles of kymography, the reader is referred to previous articles (7, 8) and to the papers of Hirsch and Johnson (9).

[1] Presented before the Radiological Society of North America at the Twenty-second Annual Meeting, at Cincinnati, Nov. 30–Dec. 4, 1936.

[2] Roentgen kymographs and kymoscopes are manufactured in this country by the Liebel-Flarsheim Company, Cincinnati, Ohio.

Figure 3 is a kymogram of a normal heart. Each frame is a record of the movements of the small area on the heart

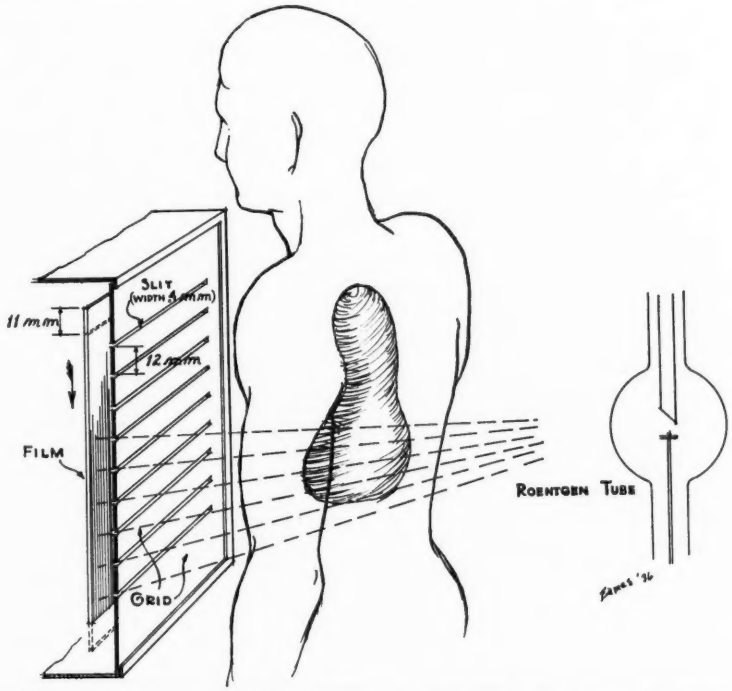

Fig. 2. Diagrammatic sketch of kymograph. For cardiac work we prefer the arrangement whereby the grid is fixed and the film is moved downward behind the grid during a single continuous x-ray exposure. (Modified after Stumpf.)

border which was opposite a slit during the time the heart filled and emptied. Each wave is one cardiac cycle. The lower leg of each wave is the record of diastole and the upper leg, of systole.

Since the slits in the grid are equally spaced and the film moves at a uniform rate, all points on any wave that are equidistant from a white line at the bottom of any frame, occurred at the same instant. By measuring these distances in various frames, it is thus possible to determine the time relationship of the movements that occur in the different cardiac chambers.

For example, ventricular systole begins at the peak of the waves and moves medially. If we measure this same distance from the peak to the white line at the bottom of the frame in the aortic area, we see that the aorta is filling outward as the result of the ventricular contraction. Other methods for determining the time occurrence of movements in the various cardiac chambers and great vessels are mentioned in references (8) and (10).

At this point we should like to mention that in 1926 Dr. W. Edward Chamberlain and William Dock (22), using Dr. H. E. Ruggles' cinematograph, were able to make 16 x-ray films of the heart in one second. They then superimposed these films in their chronological sequence and by measuring the change in position of a series of linear points on the heart border, they were able to construct a graphic curve which was a record of the movement of these points on the heart border as it filled and emptied. It is to the credit of this ingenious experiment that Dr. Chamberlain's curves are practically of the same shape and possibly more ac-

curate than those recorded by the present-day kymograph (Fig. 4).

The following illustrations are a few instances in which we feel that kymography is of value in the clinical study of heart disease. Confidence in any new procedure is gained only through precedents which are established by following the patient to the operating room, by postmortem examinations, and by comparing one's results with those obtained by others. The pursuit of these objectives is always difficult and requires time before they can be agreed upon and accepted. We have freely consulted the contributions of Wilke (11), Fetzer (12), Bicken-

Fig. 3. Roentgen kymogram of normal heart: (*a*) Peak of aortic wave attained just after onset of ventricular systole; (*b*) Waves produced by pulmonary artery; (*c*) Maximum systole at trough of wave; (*d*) Maximum diastole at peak of wave; (*e*) Notch produced by systole of auricle; (*f*) Wave produced by auricular appendage; (*g*) Trough of auricular wave corresponds to peak of ventricular wave; (*h*) Right lower cardiac border is formed by the right ventricle.

Over left heart border frames 1–3, descending aorta; 4–5, pulmonary artery; 6–7, left auricle; 8–14, left ventricle. Over right heart border, frames 1–4, superior vena cava; 5, ascending aorta; 6, auricular appendage; 7–10, right auricle; 11–14, right ventricle.

Exposure factors: 100 ma.; 85 kv.; 28 in. target-film distance; exposure time, one and one-fifth second.

bach (13), von Braunbehrens (14, 15), Heckmann (16), Schilling (17), Gillies and Kerr (18), and others. Stumpf and his colleagues have recently published a very excellent book which includes most of the kymographic studies done in Europe. It represents an enormous amount of work and should be consulted by all interested in this type of work.

In Figure 5-*A*, a kymogram of a pericardial effusion, note the very small cardiac motions over the entire heart border as the result of compression. In Figure 5-*B*, part of the fluid has been removed and replaced with air. The waves over the portion of the heart surrounded by fluid are small (Fig. 5-*C*). Near the fluid level the cardiac motions are larger: at the surface of the fluid very large waves are produced by the splashing fluid. Above this level the heart is surrounded by air, which permits a larger diastolic excursion as the lung is not in contact with the heart to act as a buffer. This kymogram illustrates especially well the refinement in the recording of physiological motion that can be achieved kymographically. These films also confirm the view that changes in the surroundings of the heart modify the heart action itself.

In dextrocardia (Fig. 6) the position of the heart is reversed, but the movements of the chambers and great vessels are exactly the same as in the normal heart (19). Other changes in the position of the heart produced by other conditions show, on the whole, no new problems, and their movements are unaltered.

The detection of rhythmic disturbances is a mere accident because of the short exposure time of one second, unless patients are carefully kymographed with this purpose in mind and then preferably by the technic of Cignolini (20) or Zdansky and Ellinger (21). Ventricular extrasystole (16, 19) produces a striking kymogram showing one small wave, the extra systole, followed by a large wave (Fig. 7). The large wave results from an over-distention of the ventricle produced by the prolonged filling which is recorded as a diastolic plateau. It is the prolonged filling of the ventricle that gives rise to the compensatory pause which is felt in the radial pulse. The extra-systole is not registered on the aortic waves, which indicates that the semilunar valves were not opened.

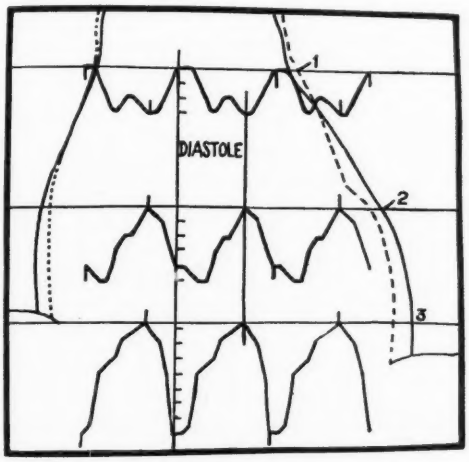

Fig. 4. "Frontal projection of the normal heart at end of diastole (heavy lines) and at end of systole (dotted lines) together with skiacardiograms at the points indicated by the numbers. The maximum auricular excursion (Point 1) is 3 mm., maximum ventricular excursion (Point 3) is 7.5 mm. Duration of diastole is nine-fifteenth second. Duration of systole is four-fifteenth second. An up-stroke marks the beginning; a downstroke, the end of systole" (Chamberlain and Dock).

Careful measurements on kymograms of normal hearts are consistent in that diastole consumes two-thirds of the total time of one cardiac cycle. Systole consumes but one-third of the time. These findings are in close agreement with those obtained by cinematography.

The electrocardiogram is of great superiority in the diagnosis of arhythmias due to its unlimited exposure time and its definite separation of auricular and ventricular movements. The electrocardiogram is a graphic record of the electrical phenomena produced in the heart muscle as it contracts and expands. Roentgen kymography is a graphic record of the movement of the heart muscle itself as it functions during the cardiac cycle. One is primarily a record of electrical impulses, the other primarily of muscle tissue. Each has advantages and limitations:

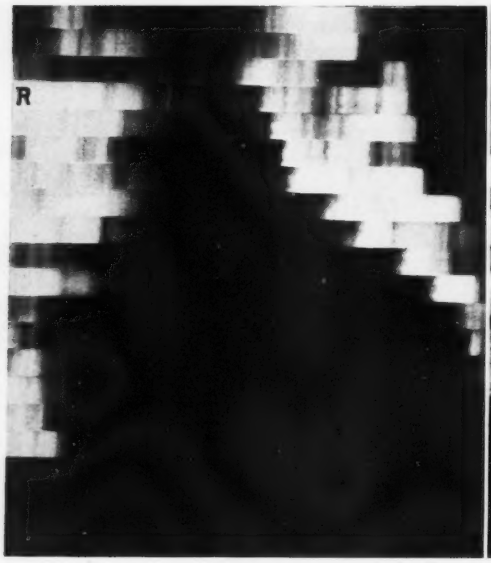

Fig. 5-*A*

Fig. 5-*B*

Fig. 5-*A*. Kymogram in pericardial effusion. Note the very small movement over the entire cardiac outline which constitutes the so-called cardiac compression syndrome described by Claude Beck. The decrease in the cardiac movement is due to an inability of the heart to expand during diastole.

Fig. 5-*B*. Diagnostic hydro-pneumo-pericardium. Pericardial sac is not appreciably thickened. Note position of fluid level and area of heart in contact with air.

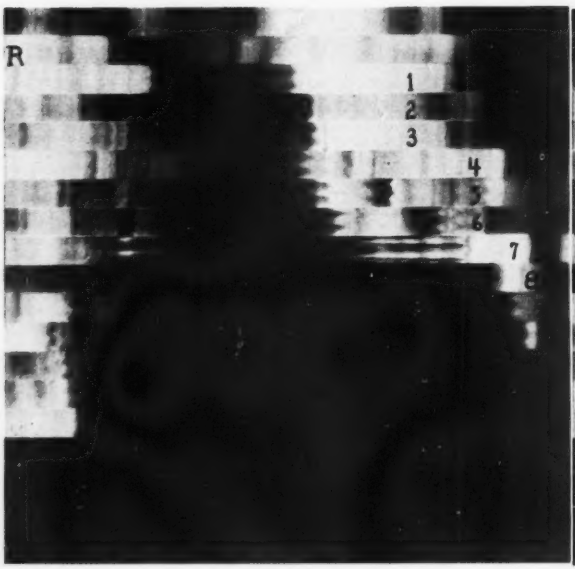

Fig. 5-*C*

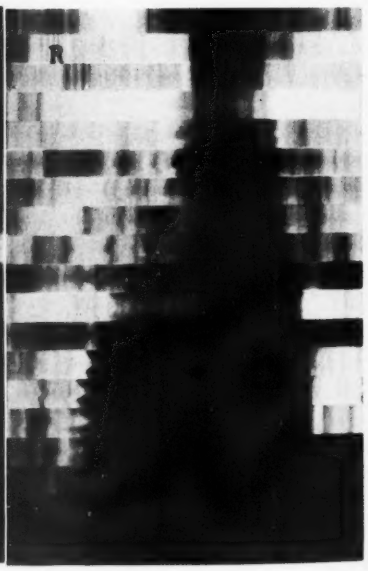

Fig. 6

Fig. 5-*C*. Kymogram made at same time as Figure 5-*B*. In frames 1–3 aortic movements are buffered by adjacent lung; frames 4–6, large movements as heart is surrounded by air; frame 7, splashing fluid level; frames 8–10, movements of ventricle gradually decrease as apex is approached.

Fig. 6. Dextrocardia. The position of the heart is reversed. The movements of the chambers and great vessels are exactly the same as in the normal heart. Compare with Figure 3.

neither replaces the other. In the kymogram of a normally functioning heart, the movement waves are of moderate size, smooth, clear-cut, and give the impression of strong, easy-going motion (Fig. 3). Figure 8 is the kymogram of a 50-year-old man. The movement waves are small, their edges are ragged due to little superimposed notches and indentations. The motion of the heart muscle is hesitant, and may we say, undecided. It has been our experience that in such patients, the electrocardiographic report will read "myocardial damage," "myocardial impairment," or a like phrase. We feel that a similar diagnosis is justified from studying the kymogram, and have been making such diagnoses for several months. As to the significance of each little notch or indentation on the waves we are not prepared to state. That is one of the many problems open for future investigation. Stumpf, Faber (23), and Hirsch have previously emphasized the value of kymography in estimating the tone and efficiency of the heart muscle.

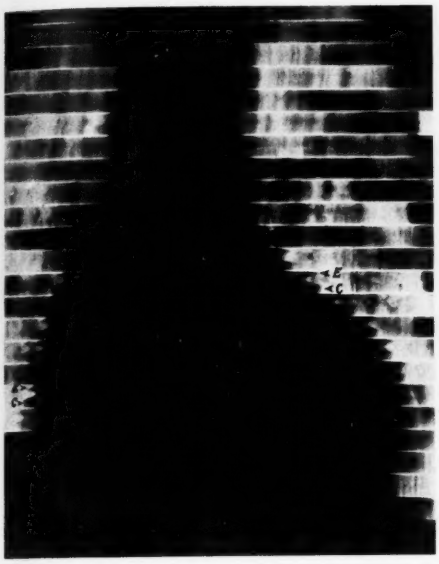

Fig. 7. Ventricular extra-systole. This patient was having repeated extra-systoles. The extra-systole is the small wave, *E*, which is following the large wave, *C*. The wave, *C*, is the record of the compensatory pause produced by a preceding extra-systole that is not shown in this record.

In decompensated hearts (17, 19, 23), a similar but poorer type of cardiac motion is recorded (Figs. 9-*A* and 9-*B*). The waves are smaller and more ragged. After digitalization and the regaining of compensation, the motion of the heart is improved as shown by the larger, more forceful, and more clear-cut waves, together with a decrease in heart size.

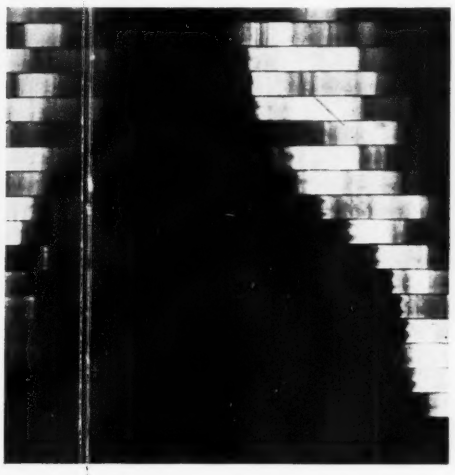

Fig. 8. Kymogram of moderately advanced myocardial impairment. Patient is a 36-year-old colored salesman whose chief clinical symptoms were dyspnea, precordial discomfort, and palpitation on exertion. Blood pressure 180/140. Serology negative. The electrocardiogram revealed moderate myocardial damage and a common type of bundle branch block. Note the small amplitude of ventricular motion and the small superimposed irregularities on the waves of the left ventricle.

Thus far we have made a kymographic diagnosis of cardiac infarction in six instances. The kymographic detection of cardiac infarcts has been previously described by others (8, 13, 14, 15). In all cases the history and electrocardiograms were characteristic of a coronary infarct. Two cases were confirmed on postmortem examination. The kymogram in Figure 10-*A* shows that the area of infarction possesses no motion as shown by the straight lines, with areas of adequate motion on either side. This patient is a man, 63 years of age, who experienced an

attack of severe precordial pain ten days prior to admission. The electrocardiogram showed evidence of coronary

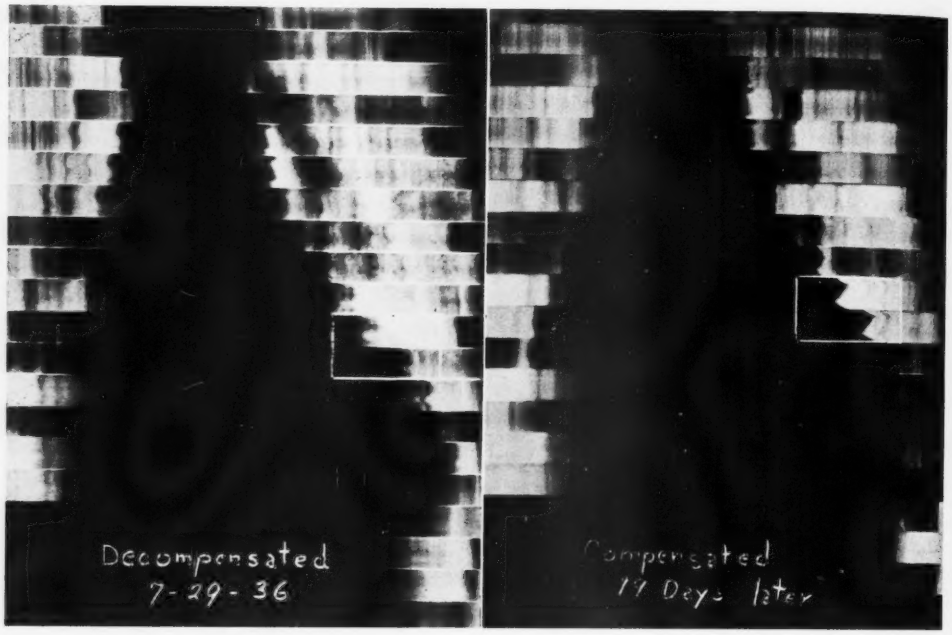

Fig. 9-*A* Fig. 9-*B*

Fig. 9-*A*. The heart in decompensation. The amplitude of ventricular contraction is small. The ventricular waves are ragged, indicative of a poorly functioning myocardium.

Fig. 9-*B*. The heart after regaining compensation. The patient was fully digitalized. The contractions of the left ventricle are now larger, more forceful and clear-cut. The heart is smaller. Both films made with the same technic.

occlusion. Repeated kymograms showed this persistent defect as demonstrated in Figure 10-*B*, made 12 days later or 22 days following the occlusion. Note the improved cardiac tone with the return of slight motion at the site of infarction.

It is hoped that in the future kymography may prove of value as a means of demonstrating areas of cardiac infarction. Paul White (24) states that, "The commonest site of cardiac infarction is the descending branch of the left coronary artery and as a result has been called the 'artery of sudden death' or 'the artery of cardiac infarction.' The second most likely spot for infarction is the posterior wall of the left ventricle near the base, due to occlusion of the right artery." The posterior descending branch of the left coronary artery passes along the interventricular sulcus on the anterior surface of the heart and around the apex and up the posterior surface for a short distance. Thus it is quite possible to make kymograms in positions which will outline this portion of the heart muscle.

The kymogram shown in Figure 11-*A* is that of a 38-year-old man who experienced severe precordial pain three days prior to the making of the film. Note the small movement of the entire left ventricle, a finding which Stumpf (19) states occurs with coronary infarction. The patient died three days later, and at postmortem a fresh infected infarct was found in the left ventricular wall near the apex (Fig. 11-*B*). There also was an older softened infarct in the posterior wall of the left ventricle just below the aortic valve: only a small segment of uninvolved cardiac muscle separated these infarcts at one level.

These findings explain the poor movement of the left ventricle.

These two cases illustrate that each heart is an individual problem and must be analyzed and studied as such, which requires experience in this field.

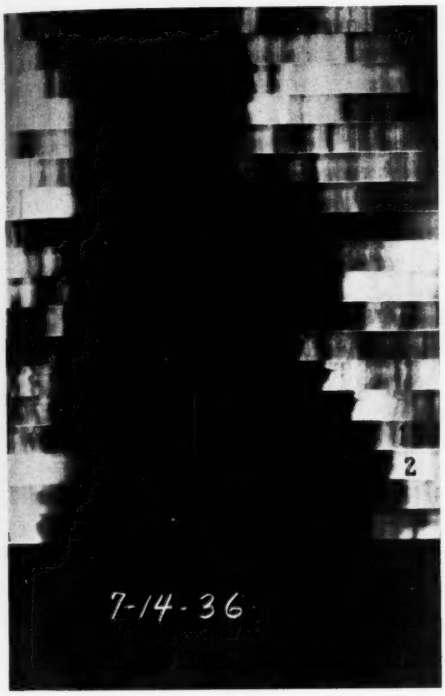

Fig. 10-*A*. Kymogram demonstrating an area of cardiac infarction. The area of cardiac infarction is recorded in frames 1 and 2. This area is without motion as shown by the straight lines with areas of adequate motion on either side.

Following a suggestion by Dr. Merrill Sosman, of the Peter Bent Brigham Hospital in Boston, we undertook a critical study of the movements of the ascending aorta in patients with hypertension, arteriosclerosis, and syphilitic aortitis to determine whether or not they could be differentiated kymographically. The chart showing the results of this study is seen in Table I. Our observations are in accord with those expressed by Stumpf (19) and others, and are briefly summarized as follows:

1. Hypertension alone does not produce increased movement of the ascending aorta.

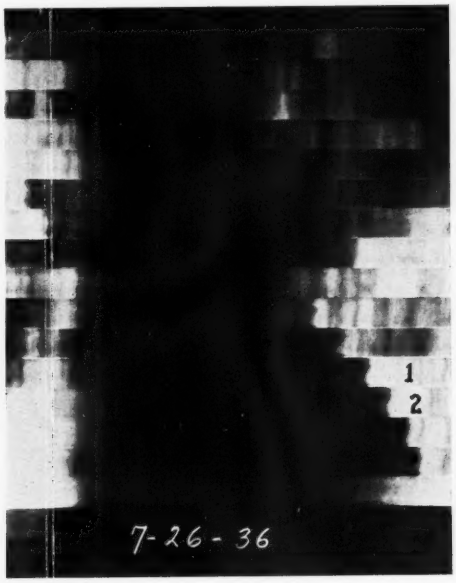

Fig. 10-*B*. Kymogram of same patient made 12 days later and 22 days following the coronary accident. It shows an improved cardiac tone with a return of slight motion at the site of the infarction.

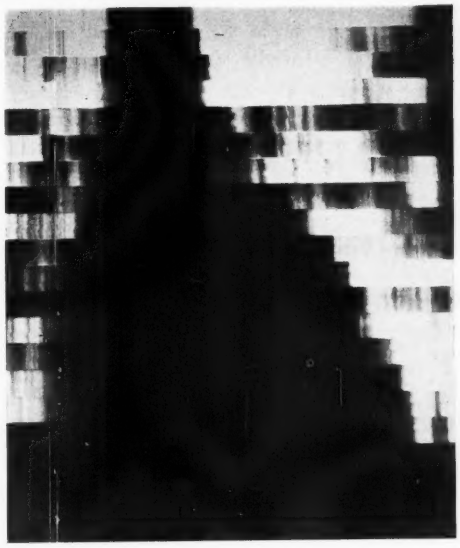

Fig. 11-*A*. Kymogram made three days following coronary occlusion. It differs from Figure 10-*A* in that the movement of the entire left ventricle is greatly diminished.

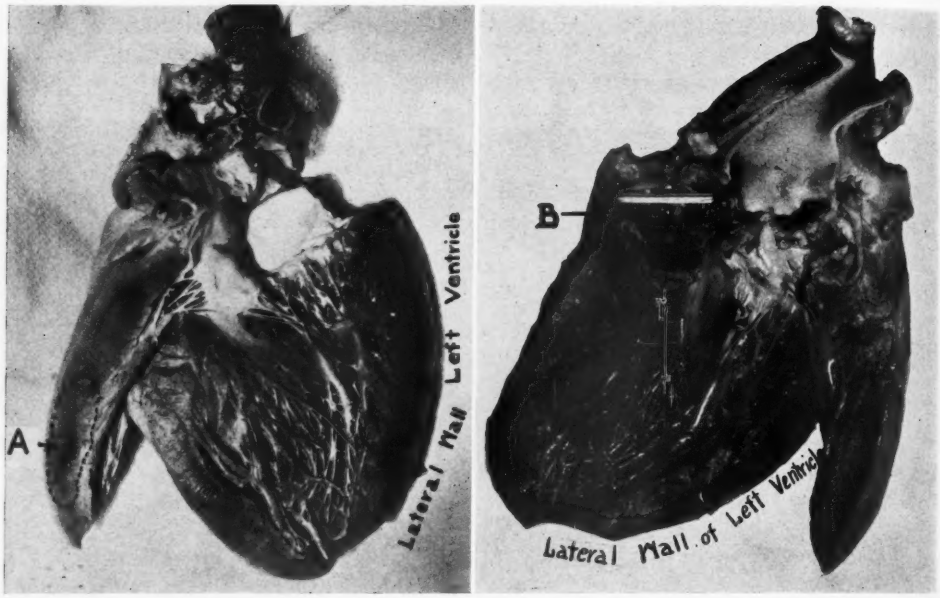

Fig. 11-*B*. Photographs of heart showing zone of fresh infarction near apex of left ventricle and a softened infarct on the posterior wall of the left ventricle secondary to an acute bacterial endocarditis. *A*, fresh infarct; *B*, old softened infarct.

2. Arteriosclerotic changes produce large movement waves over the ascending aorta which for the most part are the result of a shift in the position of the aorta during a cardiac cycle, just as a loop of garden hose tends to straighten out as water is suddenly forced through it. Kymograms made in the right and left anterior oblique positions are necessary to distinguish this type of positional change from expansile motion seen in syphilitic aortitis. In motion due to positional change both sides of the aorta shift in the same direction at the same instant. In expansile

TABLE I.—MOVEMENTS OF ASCENDING AORTA

Diagnosis	No.	Age	Increased Motion of Ascending Aorta	Type of Wave over Ascending Aorta
Normal Hearts	50	Youngest, 18 Oldest, 67 Average, 34	0	
Arteriosclerotic Heart Disease	25	Youngest, 44 Oldest, 83 Average, 58	22	Not distinctive. Due to shifting position of aorta.
Hypertensive Heart Disease (without complications)	25	Youngest, 29 Oldest, 74 Average, 52	3	Not distinctive.
Syphilitic Aortitis	50	Youngest, 28 Oldest, 70 Average, 44	Total, 22 Slight, 7 Large, 15	Not distinctive. In young adults waves may be pyramidal. Expansile.

motion the two sides of the aorta bulge outward at the same instant and move medially together.

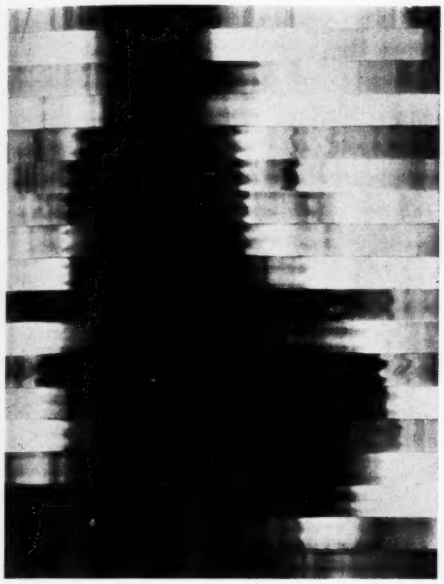

Fig. 12. Syphilitic aortitis. In nearly all cases of definite syphilitic aortitis there is observed the prominent bulging of the ascending aorta to the right. Kymographically the presence of large aortic waves in this area is most suggestive of syphilitic involvement in individuals of 40 years of age or under, even in the posterior anterior view. This patient was a 20-year-old colored female who complained of dyspnea and substernal pain. Serology 4 plus. Blood pressure 110/70. She had received antisyphilitic treatment for the past two years.

3. Syphilitic aortitis (Fig. 12) gives rise to large movement waves in less than 50 per cent of the cases diagnosed clinically. These waves are not distinctive from those seen in arteriosclerosis. The presence of large waves over the ascending aorta in adults below forty is most suggestive of syphilitic aortitis, and may be considered as such kymographically.

In the differential study between arteriosclerotic changes in the aorta and those produced by syphilis, one of us (H. A. McC.) first suggested that the large movements over the ascending aorta seen in syphilitic aortitis were the result of a destruction of the elastic fibers in the media of the vessel wall. This permits these portions of the aorta involved to bulge outward a distance farther than normal during aortic filling. Figure 13 is a photomicrograph of a section taken from a case of syphilitic aortitis which showed, kymographically, enlarged movements over the aorta. The elastic fibers are disrupted and broken.

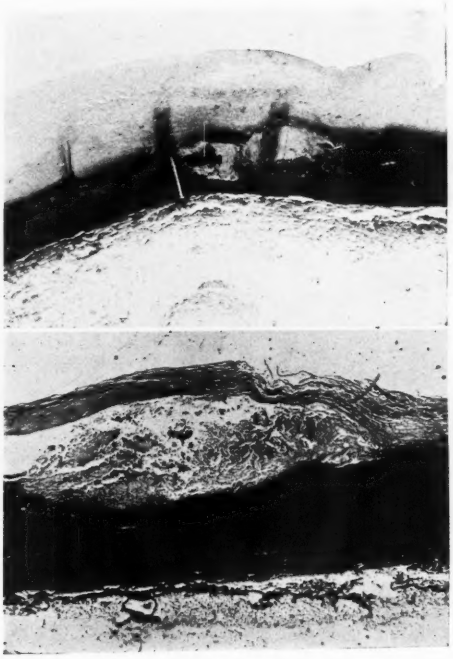

Fig. 13 (*upper*). Photomicrograph of section of aorta involved by syphilitic changes. The elastic tissue is stained black. Two large white scars interrupt the elastic tissue of the media near the center of the picture. The media shows fibrous thickening.

Fig. 15 (*lower*). Photomicrograph of arteriosclerotic changes in aorta, elastic stain. The black elastic fibers of the media are intact. In the intima on the left-hand side, there is a large arteriosclerotic plaque which contains calcium and cholesterin crystals.

In arteriosclerosis (Fig. 14) the elastic fibers remain intact but are unable to function normally in areas where sclerotic or hyaline plaques are deposited in the intima. These changes may be compared to an elastic band upon which a few flattened rigid objects have been cemented in the unstretched state. The portions of the elastic band under the cemented areas cannot be stretched, but the free intervening segments retain their elasticity. Figure 15 is a photomicrograph made

through an arteriosclerotic plaque in the aorta and demonstrates these intimal changes with the elastic fibers of the media remaining intact. Stumpf (19) maintains that in arteriosclerosis the aorta consistently shows less movement.

Fig. 14. Arteriosclerosis. Cardiac silhouette is not enlarged, but the aorta is considerably lengthened. The large waves over the ascending aorta are produced by positional change as can be demonstrated in the oblique views. Patient is a 70-year-old woman. Blood pressure, 230/110. Serology, negative.

The kymogram in Figure 16 is that of a colored female, 29 years of age, with a hypertension of 238/130. The movements over the ascending aorta are not in excess of those shown in many normal hearts.

In the study of aortic movements certain errors in technic and interpretation should be guarded against. First, the patient must not breathe during the exposure as the movements of breathing exaggerate the aortic motion. Second, aortic movements are influenced by the pulse pressure, curve of aorta, structure of aortic wall, and by the width of the aorta. Third, oblique kymograms are necessary to distinguish between inherent expansile motion or movement due to a shifting in the position of the aorta. Fourth, it must be appreciated that the curve of aortic filling is a record of ventricular systole, and that the curve of ventricular systole must be studied before evaluating changes in the aortic waves.

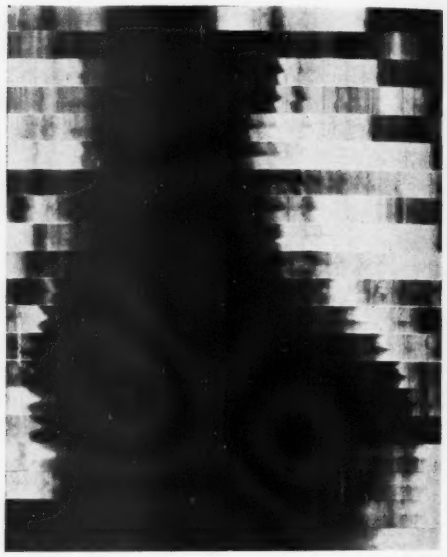

Fig. 16. Hypertensive heart disease in a young individual shows little or slight increase in movement of the ascending aorta. Hypertension itself seldom produces a noticeable increase in the size of the aortic movements. The heart is usually enlarged and the aorta is slightly widened. Patient is colored female, 29 years of age. Blood pressure, 238/130. Serology, negative.

The literature contains occasional references concerning the presence of separate liver pulsations. In pneumoperitoneum (Fig. 17) the right diaphragmatic leaf and the liver are separated by air and the movements of each can be recorded. The small pulsations at the liver are of the same shape, size, and time occurrence as those of the diaphragm and intestines. Stumpf (19) considers this as ample evidence that normally the liver does not pulsate differently from contiguous organs.

The accurate diagnosis of a cardiac aneurysm is a very difficult task even when aided by all the mechanical equipment available in the modern hospital. Von

Braunbehrens (14) first reported the kymographic diagnosis of a cardiac aneurysm. In Figure 18-*A* the usual type of chest film

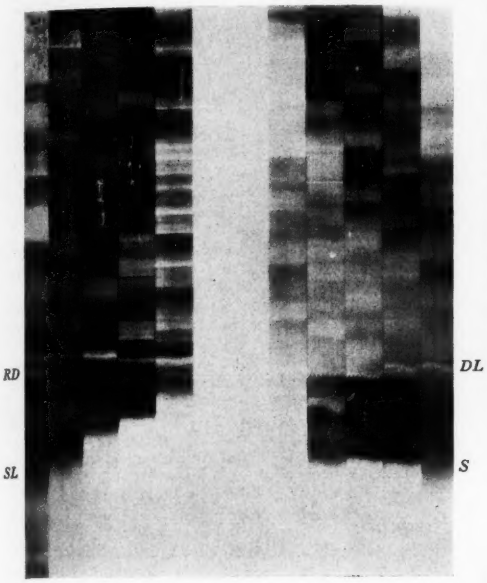

Fig. 17. Artificial pneumoperitoneum. The pulsations over the superior border of the liver are of the same shape, size, and time occurrence as those recorded by the diaphragm and stomach. *RD*, right leaf of diaphragm; *DL*, left leaf of diaphragm; *SL*, superior border of liver; *S*, superior border of stomach.

is shown, which includes the outline and size of the cardiac silhouette. On the border of the middle third of the left ventricle is a hemispherical outpouching about the size of an English walnut. Fluoroscopically, it was debated by several clinicians as to whether or not this tumefaction moved synchronously with the heart or *vice versa*. The diagnoses involved included a tumor of the heart, a tumor in the adjacent lung-field, and a cardiac aneurysm. The kymogram (Fig. 18-*B*) settled the question and established the diagnosis of an aneurysm of the left ventricle.[3]

[3] Since submitting this paper for publication, this patient died, and an autopsy was performed. Much to our surprise, a highly malignant tumor, rising from the endothelium of the pericardium was found at the site of the tumefaction, refuting the diagnosis of a cardiac aneurysm. Here again is a reminder of the extreme difficulty in distinguishing between an aneurysm and a tumor. These kymographic and pathological findings are most instructive, and will, therefore, be reported in detail in a future publication.

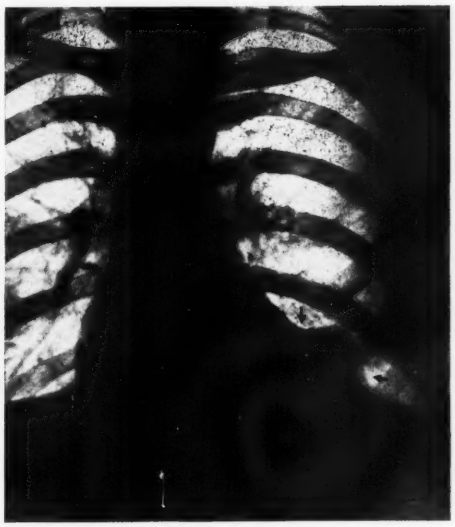

Fig. 18-*A*. Postero-anterior roentgenogram of chest illustrating the area of tumefaction on border of left ventricle which was considered as an aneurysm of the ventricle.

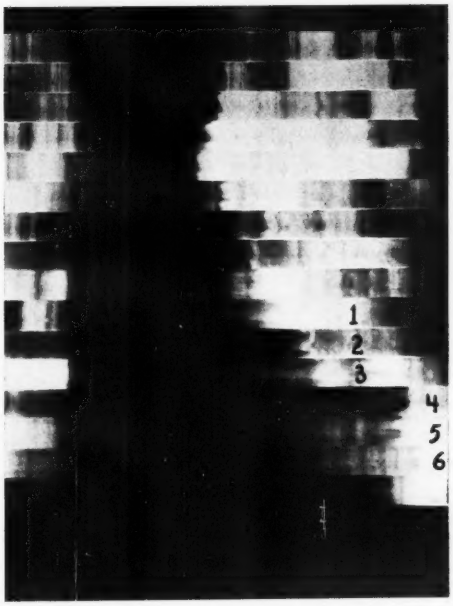

Fig. 18-*B*. Kymogram demonstrating aneurysm of left ventricle. The movements of the uninvolved ventricle are recorded in frames 1, 2, and 3. The movements of the aneurysm are in the opposite direction and are shown in frames 4, 5, and 6. The time relationship is accurately established by measuring the distance from the black line at the bottom frame over the ventricle to a particular wave and then measuring this same distance in a frame over the area of the tumor.

The tumefaction is objectively recorded as bulging outward (laterally) at the same moment the remaining portion of the ventricle is in the medial position at systole. During diastole, the tumefaction is in its medial position (trough of the wave), while the other portions of the ventricle are in the lateral position (peak of the wave).

CONCLUSIONS

In conclusion we wish to emphasize a few kymographic principles that have been of help to us in interpreting these films:

1. Kymography is primarily a picture of the physiological motion of an organ or structure.

2. The kymogram will be varied from the normal only insofar as a heart lesion will alter the movement of the heart muscle.

3. Movements of the heart are altered by certain diseases of the valves, by changes in the pericardium, alterations in the pericardial contents, changes in the heart muscle producing variations of muscle tone and efficiency, and occasionally, by changes of rhythm.

4. The clinical evaluation of kymography at present is difficult because of its infancy and the relatively few men using the procedure. It must be considered as another aid in the diagnosis of heart disease and viewed somewhat modestly as helpful and supplementary to the average heart diagnosis, but not accorded too much importance. In a few instances kymography will be the means of establishing a difficult and obscure diagnosis.

5. The assembling of facts and their comparison with clinical methods is the important problem of the future.

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DISCUSSION

DR. C. L. GILLIES (Iowa City, Iowa): As Dr. Scott has told us, the principle of roentgen kymography is not new. Its possibilities as a diagnostic aid in the study of the heart and great vessels have long been appreciated. The popularity that the method is beginning to enjoy is not so much due to improvement in kymographic apparatus as to increased speed in radiography, which permits using narrower grid slits and faster grid or film movement. This produces better definition of outline on the kymogram and allows the wave forms to be spread out so that they can be better analyzed. It is now possible, also, to make satisfactory lateral and oblique views not formerly obtainable.

The aid of the kymograph in the diagnosis of cardiac infarcts, certain valvular lesions, and in differentiating solid tumors from pulsating aneurysms is well established. This is not true of all disease, for while valvular and myocardial damage should produce alterations in the kymographic record, some of these changes are not now recognized or well understood. It is only through the careful study of groups of cases, such as have just been presented, that we may become familiar with and able to recognize these abnormal wave forms.

Therefore I feel that this and other papers by Dr. Scott and Dr. Moore will not only increase the interest in kymography, but that their contributions on interpretation will serve as a guide to those of us who have not had the opportunity or industry to make similar intensive studies.

DR. AUGUSTUS W. CRANE (Kalamazoo, Mich.): It is a real privilege to hear this paper and to discuss it.

I think it is somewhat confusing to anyone to look at the roentgenologic exposure of the kind you have been seeing. Obviously, the interpretation of such views will take a great deal of time. When you think of the enormous amount of labor which has gone into the interpretation of the electrocardiogram, you can realize that the full meaning of these kymographs will not be immediately evidenced.

The original kymograph, as you know, was a single slit with the passage of the screen or the x-ray film or, at that time it was an x-ray plate—a passage of considerable length—so that you had a tracing going the entire length of the film—or, I should say, the plate. (We get so used to speaking of films!)

That gave a tracing which could be compared to the sphygmographic tracings such as Sir James MacKenzie used to make, or the tracings of the electrocardiogram.

I think if there is any one criticism which might be made of the present method it is the brevity of the curve, of the tracing. It takes in a single impulse or at the most two, unless we have a tachycardia, in which case you may get more.

It is obvious that when it comes to arrhythmias such as auricular fibrillation or heart block or extra-systoles, these tracings may give you confusing information. You could hardly recognize the true character of the beat if you happen to get the extra-systole at the time of exposure. You would have to take more than one view.

It still seems to me highly desirable that this method should be such that we are able to get curves of considerable length showing the heart in motion over a longer period of time. It has, however, the great value of showing the entire border of the heart on both sides.

It is obvious that the x-ray method is the only method whereby you can study simultaneously the muscle movements of more than one chamber of the heart. Perhaps I should not say quite that, because the sphygmographic tracings of the radial pulse at the same time you get an impulse from the jugular vein in the neck give you a polygraphic tracing for comparison. Those tracings represent, of course, the pressure impulse from the heart, something different from muscle movement.

In the electrocardiogram you get no

separation of chambers excepting the auricles and ventricles. You get the mass muscle movement in one end of the heart and the mass muscle movement at the other; or rather, you get not the movement but the electrical potential. However, by roentgen kymography if we were to rotate the patient, we could get the pulsations of the right ventricle and the left ventricle simultaneously, or the right auricle and the left auricle or the aorta, and I think there is no method yet devised which is so authoritative in distinguishing between a mediastinal tumor and an aneurysm—sometimes a matter of very great importance.

I think you have listened to a very masterly paper and in its present form it will be a very distinct addition to the examination of the heart, although we must say that there is no organ of the body which presents itself for so many kinds of examination as does the heart. We can listen to it; we can feel its pulsations and see them on the x-ray screen; we can get the electrical potential on the electrocardiogram; we can get the tracings of the venous and left ventricle tracings with the sphygmograph. Is there any other organ of the body that allows so many different types of examination?

Yet I think the internist will agree that he never knows too much about the diseased heart. For that reason I think that the cultivation of this method by the roentgenologist is fully warranted.

I am sorry that I did not express my appreciation a few moments ago of that very excellent paper on the duodenum. My attention was taken up with the primary carcinoma of the duodenum.[1]

DR. SCOTT (closing): It has been a great pleasure to hear Dr. Crane tell about his early work. It represents a truly remarkable piece of mechanical ingenuity. At the time it was started there were only two articles in the German literature, and neither contained more than a diagrammatic outline of the principles of kymography. From this inadequate description Dr. Crane constructed a superior apparatus. His records represent a great improvement. His work commands our highest respect.

I am much pleased with what Dr. Chamberlain had to say about kymography and its possibilities. His interest in cinematography makes it possible for him to evaluate better the practical applications.

We appreciate also Dr. Gillies' discussion and are looking forward to his further reports.

I regret that Dr. Moore has been unable to be here and to participate in this discussion.

[1] Malignancy Involving the Duodenum. Allan Tuggle and Sidney Weintraub. To be published later.

THE USE OF PENTOBARBITAL SODIUM FOR ROENTGEN NAUSEA AND VOMITING[1]

By WALTER C. POPP, M.D., Section on Therapeutic Radiology, *and* MELVIN W. BINGER, M.D., Division of Medicine, the Mayo Clinic, *Rochester, Minnesota*

NAUSEA and vomiting as a complication of roentgen therapy has been the concern of the radiologist since the advent of this mode of treatment. The causes of roentgen sickness are not definitely known; whether it is a toxic effect on the higher centers or a reflex action over the sympathetic or parasympathetic system has not been absolutely established. To overcome this complication many therapeutic agents have been tried but, because of their failure or their expense, they have fallen into disuse. As an empirical measure one of us (M. W. B.) prescribed a sedative to be taken at each session of treatment. As a result of this trial there was definite evidence of relief from the severe sickness which commonly attends roentgen therapy.

Following this experience, many different sedatives were tried in the hope of finding one with a sedative action sufficiently rapid that the patient might be under fairly good sedation during the interval in which radiation sickness usually occurs. After the experimental use of several drugs, pentobarbital sodium was decided upon because of its rapid sedative effect. The successful use of barbiturates to overcome vomiting, sea sickness, or migraine were reported by Wolfram as early as 1906. Experience has also taught that these drugs relieve the nausea, vomiting, or convulsions of uremia due either to primary nephritis or to severe terminal hypertension. In general, they are used extensively for relieving migraine, epilepsy, anorexia nervosa, and many of the functional disorders of the nervous system. As with all barbiturates, pentobarbital sodium is a powerful hypnotic. Its action is chiefly central, and in effect it is a depressant to cerebral activity and diminishes sensory irritability in proportion to the amount administered. It is difficult to say whether or not the drug has a direct action on the autonomic nervous system other than through central association.

Because the majority of our patients are ambulatory, it was rather difficult to determine the best method of administration. Very few of the patients were hospitalized, so that oral administration was rather difficult. If a patient took the drug before treatment, there was considerable sedation at the termination of treatment and the patient could not be permitted to return to his or her living quarters unattended. If the capsule was prescribed after treatment, nausea and vomiting frequently seemed to be precipitated by the ingestion of the capsule itself. For a time two capsules of one and one-half grains (0.097 gm.) each were given by rectum; this seemed to yield the best results and the method of administration of the drug was therefore not responsible for the vomiting. Through the courtesy of the manufacturer of this drug we were able to procure a large number of rectal suppositories containing 3 grains (0.2 gm.) of pentobarbital sodium and, after the early trials, these were prescribed almost routinely. In twelve cases suppositories containing 4 grains (0.24 gm.) of pentobarbital sodium were used, but in practically every case the sedative effect was too great and it became necessary to resort to smaller doses of the drug. Since practically every adult patient can tolerate 3 grains of the drug by rectum, we have concluded that this dose is sufficient in the average case (2).

Richards and Peters have recorded their results with pentobarbital sodium or "nembutal" in 40 cases, and they felt that in

[1] Read by Dr. Popp before the Radiological Society of North America at the Twenty-second Annual Meeting, at Cincinnati, Ohio, Nov. 30 to Dec. 4, 1936.

the majority of instances the use of this drug is definitely indicated. Our further experience coincides with theirs in that a very small percentage (probably 1 or 2 per cent) of patients do not tolerate the barbiturate preparations. Trostler reported three cases of porphyrinemia and porphyrinuria as a complication to the administration of barbiturates in conjunction with roentgen therapy. In 275 cases we have seen no complication whatever and, except for the problem of over-dosage, as found in 12 cases, we have observed nothing that could be regarded as a contraindication. With the exception of two cases of brain tumor, we have selected for this report cases in which large doses of roentgen rays were to be given to some part of the thorax or abdomen: in our experience it is in this type of case that roentgen sickness almost always occurs.

In this study 275 patients were given pentobarbital sodium either by mouth or by rectum. Of these 275 cases, however, only 175 are included in this report; the other 100 had to be discarded because of incomplete information, either because the patient did not use the drug routinely or because he was unable to give satisfactory information concerning its effect.

Of the group of 175 patients, 27 were treated with roentgen rays generated at 200 kv., and 148 were treated with roentgen rays generated at 135 kv. Of the patients treated at high voltage (200 kv.), four received pentobarbital sodium by mouth, 23 by rectum. Of the 148 patients treated with moderate voltage (135 kv.), 35 received pentobarbital sodium by mouth, 95 by rectum, and 18 by both oral and rectal administration.

Of the 27 patients treated at high voltage, 14 were treated for carcinoma of the cervix, one for cord tumor, ten for malignancy of the abdomen, and two for brain tumor. Of the 14 patients treated for carcinoma of the cervix, 11 received six sessions of treatment; three, more than six sessions. One received pentobarbital sodium by mouth, with complete relief of nausea and vomiting. Of 13 who received pentobarbital sodium by rectum, seven obtained complete relief of nausea and vomiting, and six had only moderate nausea.

The one patient treated for cord tumor had six sessions of treatment. This patient received pentobarbital sodium by rectum and had only moderate nausea.

Of the ten patients treated for malignancy of the abdomen, six received six sessions of treatment and four received more than six sessions. One patient, who received pentobarbital sodium by mouth, was completely relieved of roentgen sickness; of the nine other patients, who received pentobarbital sodium by rectum, four derived complete relief, three had only moderate nausea, but the symptoms of the other two apparently were not influenced.

Each of the two patients treated for brain tumor received six sessions of treatment. Both were given pentobarbital sodium by mouth, one deriving complete relief and the other having only moderate nausea.

Of the 148 patients treated at moderate voltage (135 kv.), 110 were treated for carcinoma of the breast, 13 for lymphoblastoma, 18 for malignancy of intra-abdominal structures, six for carcinoma of the testis, and one for arthritis. Of the 110 patients treated for carcinoma of the breast, three received three sessions, 100 received six sessions, and seven received more than six sessions of treatment. Of this group, 25 received pentobarbital sodium by mouth, with complete relief in 14 cases, moderate nausea in three, nausea with slight vomiting in three, and with no relief in five. Sixty-eight of the 110 patients received pentobarbital sodium by rectum, with complete relief in 44 cases, moderate nausea in seven, nausea with slight vomiting in 11, and no relief in six. The remaining 17 patients in the group received pentobarbital sodium by mouth, and then later by rectum, with complete relief in 14 cases and moderate nausea in three.

Of the 13 patients treated for lymphoblastoma, one received six sessions of treat-

ment, 12 received more than six sessions. Of this group, three received pentobarbital sodium by mouth, two with complete relief and one with only moderate nausea. The remaining ten received pentobarbital sodium by rectum, with complete relief in four cases, moderate nausea in three, and nausea with slight vomiting in three.

Of the 18 patients treated for carcinoma of the abdomen, two received three sessions; 12, six sessions, and four more than six sessions of treatment. In this group, seven patients received pentobarbital sodium by mouth, with complete relief in two cases, moderate nausea in one case, nausea with a slight amount of vomiting in one, and no relief in three cases. Eleven patients received pentobarbital sodium by rectum, with complete relief in seven cases, moderate nausea in two, nausea with slight amount of vomiting in one case, and no relief in one.

Of the six patients treated for carcinoma of the testis, all received more than six sessions of treatment. In this group, five received pentobarbital sodium by rectum, showing complete relief in four cases and moderate nausea in one case. One patient received pentobarbital sodium by mouth, later supplanted by pentobarbital sodium by rectum; complete relief was obtained. The one patient treated for arthritis received six sessions of treatment; pentobarbital sodium was given by mouth, with complete relief.

Of the total patients in this series, 43 were given their first two sessions of treatment without pentobarbital sodium, but the remaining sessions of treatment were given with pentobarbital sodium. Of this group, 27 were very markedly improved with pentobarbital sodium, but 16 showed very little change in the roentgen reaction.

Of the total patients, 18 received pentobarbital sodium by mouth for the first several days and showed considerable roentgen reaction. The oral administration of pentobarbital sodium was supplanted by rectal administration and 17 patients showed complete relief, with no change in one case.

Only seven patients in this series gave evidence of too much sedation and five of these had been given 4 grains of pentobarbital sodium by rectum. This indicates that probably only two patients in the entire series of 175 showed too much sedation on an average dose.

The 10 per cent of failures occurred mostly in those cases in which sedation was not adequate. It may be assumed, therefore, that with adequate sedation or by alteration in the method of administration, at least a part of these failures might be overcome.

SUMMARY AND CONCLUSIONS

Roentgen sickness is an annoying complication following roentgen therapy. Careful study of 175 patients who had received pentobarbital sodium, in all of whom nausea and vomiting was expected to occur after treatment, revealed that 61.1 per cent received complete relief from roentgen sickness, 18.3 per cent had only moderate nausea, 10.9 per cent had nausea with very slight amount of vomiting, and and 9.7 per cent obtained no relief. We found that the administration of 3 grains (0.2 gm.) of pentobarbital sodium as a suppository immediately following a session of treatment was most successful. Since pentobarbital sodium is easily available, inexpensive, easily administered, and in our experience without harmful effects, we feel that its use in controlling roentgen nausea and vomiting is definitely indicated.

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DISCUSSION

DR. I. S. TROSTLER (Chicago): In view of the fact that mention was made of my recent warning relative to the use of the barbiturates during the application of roentgen therapy, may I state that I do not think that the cases I reported in any sense are comparable to the administration of a single dose of the drug mentioned by the essayists.

The cases I reported as having shown erythemas during the administration of this kind of medication were taking allonal as a general sedative and the patients were all more or less under the influence of that drug. They all had sufficient effect of that drug to quiet and control nervous manifestations of thyrotoxicosis or of menopausal neuroses. I have heard of one more such instance—of the production of erythema under similar circumstances—since I came to Cincinnati and I wish to reaffirm my warning.

DR. WALTER C. POPP (closing): I quite agree with Dr. Trostler that a number of patients will develop a light sensitivity as a complication while using barbiturates. It is my impression that this number of patients is small and when porphyrinuria and porphyrinemia develop, it is usually after prolonged use of the drug.

In our experience with 275 cases, using one of the barbiturates, no such complication has been seen.

HEAT AS A SENSITIZING AGENT IN RADIATION THERAPY OF NEOPLASTIC DISEASES[1]

By WILLIAM H. MEYER, M.D., Professor of Radiology in the New York Post-graduate Medical School and Hospital of Columbia University,

and

ARTHUR MUTSCHELLER, PH.D., Physicist and Instructor of Physics in the New York Post-graduate Medical School and Hospital of Columbia University, *New York City*

PART I—INTRODUCTION

THE relatively greater sensitivity of certain types of neoplasms, as compared with the neighboring normal tissue, is undoubtedly an all-important factor in the successful treatment of certain malignant diseases.

The regression obtained by means of radiation therapy in practically all of the various types of lymphomas is, of course, ascribable to the relatively greater radiosensitivity of these lesions, and, therefore, the dosage can be kept well below that which might result in serious damage to normal tissue.

The difficulty arises when a given pathologic process is resistant to radiation therapy with a sensitivity approaching that of neighboring normal tissue. Unfortunately, the latter is all too often true in most of the adult types of carcinoma.

Of the different methods suggested to increase the sensitivity of the more radioresistant types of neoplasm, the thought has occurred to the writers that heat might be employed as a simple and practical sensitizing agent.

In reviewing the literature, we came upon an article by Charles Miller (1) in which, by the combined use of radiation therapy and diathermy, a claim of the more beneficial utilization of x-radiation, with better resorption of destroyed tissue, is made. In another article by E. Dubowy (2), on the effect of temperature on the biological reaction of x-rays, but little influence on the larvæ of *Drosophila melanogaster* is admitted.

In view of the foregoing, we turned our attention in this direction. Furthermore, there have been some rather extravagant claims made by manufacturers of diathermy and short wave machines. Above all, we had a strong desire to determine whether or not heat can be employed to increase the sensitivity and thereby the effects of radiation therapy of neoplastic disease.

DIRECT HEATING METHOD

Our first effort was to determine, if possible, the influence of direct heat application during radiation therapy. For this purpose, a heating unit was devised in which reasonably accurate thermometric measurements could be made. The heating unit consists of a circular ring of bakelite (Fig. 1) about one and one-half inches in diameter and two millimeters thick. The ring, supplied with inlet and outlet tubes at opposite sides, is covered with thin sheets of celluloid, forming a flat, disc-like chamber. Various tests revealed the fact that this disc, when filled with water, showed an absorption equal to about 0.25 mm. of aluminum when from 100 to 130 kilovolts with no filtration was employed.

Direct reading thermometers were incorporated with the mercury bulbs close to the inlet and outlet ends of the heating unit. By experimentation we found that a patient could tolerate for a minimal period of ten minutes, a temperature of 115 degrees Fahrenheit, measured in the circulating water at the inlet thermometer. At

[1] Read by title at the Twenty-second Annual Meeting of the Radiological Society of North America, at Cincinnati, Nov. 30–Dec. 4, 1936.

The physical experiments were conducted with a Westinghouse short wave machine. It was through the kind co-operation of this company that this work was made possible. Some of the expense incurred in the treatment of deserving indigent neoplastic cases was met through a fund supplied by the St. Mark's Ladies' Aid Society.

the outlet, a temperature of 112 degrees was recorded with, therefore, a loss of three degrees in the heating unit attached to the patient.

EXPERIMENTAL ERYTHEMA

The establishment of biological proof is difficult, so, therefore, the interpretation of our results must depend, in the main, upon clinical observation.

Though our experience is not as yet sufficient to warrant us in drawing definite conclusions, our experiments would indicate that very little dosage is required to produce a given radiation effect when treatments are applied through the heater at the temperature above indicated. In other words, when heat is simultaneously employed, a so-called skin erythema dose can be administered in considerably less time or with less intensity of radiation. We found that from one-third to one-half the quantity of radiation administered through the heater is sufficient to produce a reaction similar to that resulting from a full unit erythema dose directly applied without heat with a similar quality of radiation.[2]

THE TREATMENT OF SUPERFICIAL LESIONS

Using the foregoing as a guide for procedure, we treated certain selected cases of superficial epithelioma with the dosage one-half of that routinely used by us in the continuous massive method of application.[3] This method of treatment was chosen in preference to the cumulative, since we felt that we had the greatest experience along these lines. Only those cases in which the closest coaptation of the heating unit was possible were suitable for this type of treatment.

[2] The skin erythema dose, as applied in our department with unfiltered rays at 130 kilovolts, is equivalent to 350 r continuous radiation with an output of 70 r per minute at a 40 cm. skin-focus distance. The quality of radiation is represented by a half value intensity of 1.75 mm. of aluminum (measured by ionization).

[3] In our massive dose method we applied on an average of ten erythema doses continuous radiation, at 140 r per minute to areas from one-half to three-quarters of an inch in diameter, at 29 cm. skin-focus distance.

Our first six cases so treated would indicate that, with this curtailed dosage with the heater, the end-results were as satisfactory as in those cases in which the more massive dosage was applied. The differences observed were that there was less local reaction and little or no tendency to ulceration with scab formation; the lesions, therefore, regressed and disappeared with but little of the inflammatory reaction previously observed.

THE POSSIBILITY OF HEATING DEEPER TISSUES AS A SENSITIZING AGENT IN DEEP RADIATION THERAPY

The problem of applying heat to deeper-lying tissues (and lesions) is far more difficult than the method of surface application as above described. The comparatively recent introduction of short wave therapy appears to offer a solution to the problem. However, with respect to the method of application as well as to the question of heat concentration, there are uncertainties which require clarification. It, therefore, becomes necessary to conduct a series of experiments which short wave therapy before this method can be logically combined with radiation therapy.

The more important questions under consideration are the following:

1. What is the most suitable method of applying electrodes?
2. Under what conditions can the greatest degree of heat concentration in the deeper structures be obtained with minimal effect on the surface?
3. What is the influence of short wave therapy on different types of structure, such as water and fatty substances, in different positions with relation to the electrodes?
4. What arrangement forms the most suitable method of combining short wave therapy and radiation therapy?

EXPERIMENTS IN SHORT WAVE THERAPY

Diathermic currents, of frequencies between 500,000 and 2,000,000 cycles per

second, produce heat, depending on the resistance of the substance and the current passing through it; in the sence of Joule's law, it is proportional to RI^2. Hence, the resistance in the path of the current causes its dissipation into heat and, therefore, contact between the electrodes and the patient is usually made directly and with the aid of soap lather or saline solution which, in order to be effective in reducing resistance losses, should have a conductance better than that of a 10 per cent KCl solution (3).

Evidence and clinical observations point to the fact that, with short wave frequencies of from 2 to 10 million cycles per second, the heating is not caused by the direct conduction of current in the same way as with diathermic frequencies, but that the rapidly changing field causes the production of local currents in the tissues which, in the manner of the production of Eddy or Foucault current, are locally dissipated into heat.

This is made plausible by the well-known fact that the flow of electrical current in a composite medium is concentrated in the medium having the highest conductance, and that it distributes over the largest volume offered by the conducting substance. Short wave fields, however, traverse most substances more uniformly, but react, in respect to heat production, differently by producing under certain conditions, more heat in a better conducting substance than in one having a higher electrical resistance. Therefore, a high resistance medium in series with a better conducting substance might not cause any great loss of energy, but rather, a concentration of energy dissipation in the substance having the lower electrical resistance.

Under some conditions, therefore, an air space or a very high dielectric between the electrodes and the patient would be permissible or even required, and it would seem that one of the principal advantageous features of short wave therapy is the possibility of confining the heat dissipation of electrical energy upon one given substance by placing in series with it media having a lesser dissipating power for electrical energy than the substance to be heated.

The earliest summary of experiments on electrical high frequency fields of between 3 to 12 meters wave length applied to plants and animals seems to be that of Georges Lakhovsky (4). The plants were placed, without using electrodes, in the field of an inductance winding. J. W. Schereschewsky (5) placed small animals in a box-like arrangement of which two sides comprise the plates of a condenser, thus subjecting the animals to the oscillating field between the plates. A. Esau (6) and E. Schliephake (7) showed the use of spaced electrodes without making contact and H. R. Hosmer (8) described the heating effect of high frequency fields with cold electrodes spaced by air gaps from the object to be heated.

Therefore, the air space between electrodes and the parts to be treated appear to be an important condition to the possibility of utilizing the action and the effects that are specific of the ultra-short wave lengths. But in spite of these apparently distinctive properties of short wave frequencies and a lack of evidence that the particular frequencies alone are responsible for specific or selective effects (7), the short wave currents are extensively applied in clinical practice with the same types of electrodes and in the same manner as the older diathermic currents and electrodes. Electrodes are manufactured and sold, and instructions for their use are given with them which are not apparently in conformity with the specific electrical requirements and thereby practically all the advantages of short wave over ordinary diathermic therapy are lost. A series of experiments described in the following are intended to elucidate some of the principles and the results obtainable under various conditions of application of short wave currents.

Experimental.—The short wave generator employed for these experiments is a Hartley Circuit, and the oscillating condenser is developed so that the object to be

treated can be placed between the condenser electrodes. The entire oscillating unit is housed in a metal cabinet, and a balancing condenser, variable from the outside, is employed to balance the circuit to resonance. This condition is then indicated by a coupled circuit containing a current meter which, by maximum reading, indicates the condition of balance.

Other devices employed are a number of Hg-in-glass chemical thermometers which were previously compared in a water bath at various temperatures. A block of gelatine was prepared by dissolving 230 g. of cooking gelatine in 3,800 ml. of hot water, pouring it into a wooden trough and allowing it to stand at room temperature. The result is then a stiff jelly, and for measuring its temperature the thermometers can be easily pushed into the mass of the jelly in evenly spaced places; during the treatment the thermometers were removed. For some of the experiments, in order to enable the block to be removed from the trough, the jelly block is removed from the wooden trough by immersing the latter in hot water which causes a small quantity of gelatine near the sides to become liquid. Another medium employed is lard, which at ordinary temperature is sufficiently consistent to exhibit the same plastic properties as the jelly.

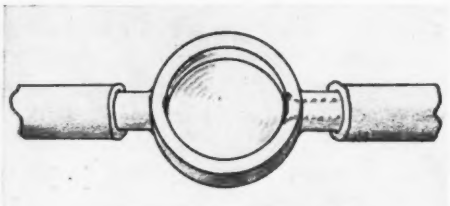

Fig. 1. Contact water heater for direct application of heating. (For a detailed description, see text.)

I. The experimental arrangement is shown diagrammatically in Figure 1. This arrangement corresponds generally to the conditions under which short wave therapy is clinically applied, and a number of manufacturers give directions that it be applied in this manner. Metal foil electrodes, either covered with an insulating substance or bare, are usually spaced from the patient's skin with felt; towels of other substances are assumed to have high dielectric properties.

The thermometers were evenly spaced and pushed down to the middle of the mass of the jelly; they were read before and after the application of the current but were *removed during the application.* After the full output of the machine had been applied for 20 minutes, there was a slightly higher elevation of temperature in the middle portion of the jelly, but from about the tenth minute on, there was profuse melting of gelatine at the sides at which the electrodes and the padding were applied. The padding also, especially if it was of starched towels, had heated very strongly.

The conclusions from this test are that if the electrodes are spaced from the medium to be treated with dielectric substances, such as felt, towels, wood, etc., then these substances dissipate and absorb a large portion of the applied electrical energy. The heating is strongest in the better conducting substances, such as wet wood and starched towels, and least in a perfectly dry felt padding. However, in a general way the appearance of the results of this method of application differs in no essential respect from that observed from the application of ordinary diathermic currents.

II. The same experimental run was made except for leaving out the padding and suspending the electrodes so that instead of the padding there was an air space between the gelatine contained in the box and the electrodes.

TABLE I

Thermometer	1	2	3	4	5	6	7
Tempt. at start	20.0	19.9	19.5	19.8	19.6	20.0	20.0
Tempt. after 20 min. run	29.0	29.6	30.0	31.0	30.0	29.2	29.3
Diff. temp. °C.	9.0	8.7	10.0	10.2	10.4	9.2	9.3

TABLE II

Thermometer	1	2	3	4	5	6	7
Tempt. at start	21.0	21.3	21.0	21.2	21.2	21.0	21.3
Tempt. after 20 min. run	26.9	28.0	28.6	29.6	28.9	27.5	27.6
Diff. of tempt.	5.9	6.7	7.6	8.4	7.7	6.5	6.3
Thermometers crosswise		28.7	29.3	29.5	28.5	26.0	
Diff. of tempt.		7.4	8.3	8.3	7.3	5.0	

TABLE III

Thermometer	1	2	3	4	5	6	7
Tempt. at start	22.9	23.3	23.0	23.0	22.8	23.0	23.3
Tempt. after 20 min. run	28.0	28.8	29.4	29.0	29.4	28.8	28.0
Diff. of tempt.	5.1	5.5	6.4	6.0	6.6	5.8	4.7

The temperature increment in the center portion of the jelly after a 20 minute run is greater than in Experiment I. Melting of gelatine at the ends started only from the fifteenth minute on. The wooden sides of the box through which the field was applied were quite warm and evidently caused the melting of the gelatine; the long sides had remained cold.

Thremometers placed transversely showed also a slight temperature increase in the center as against that at the borders.

It is to be concluded that the absence of padding (or the presence of the air gap) has a distinctly advantageous effect upon the utilization of the short wave energy absorbed in a medium to be treated, in that then, instead of being largely consumed in heating of dielectric padding, the energy is consumed to a considerably greater extent in the middle part of the jelly.

III. A still further variation from the experimental conditions of Experiment I was introduced by removing the wooden trough from around the jelly block and suspending freely the bare metal electrodes in air; thus there was then no dielectric except air between the electrodes and the jelly block.

The total temperature increase as the result of the 20-minute application of the output of the short wave generator is again slightly less, but in this experiment the maximum in the center is distinctly higher over the temperature rise of the borders and near the electrodes than it was in the previous experimental runs.

It is to be concluded from these experiments that the production of a maximum of heating in the center of a medium without also over-heating the sides through which the energy is applied, is only possible if dry air (or extremely high dielectrics) is present between the electrodes and the medium to be treated.

IV. An arrangement of the media through which the short wave length field was caused to pass, quite different from the preceding arrangements, was made for the following experiment.

In series with the gelatine jelly was placed a block of lard, as shown in Figure 2. Otherwise, the electrodes were placed with air gaps as described in Experiment III. The combined block of gelatine and lard, therefore, represents that part, of the patient to be treated, consisting of several substances, as, for example muscle layers or bone and fat, and so placed with respect to the electrodes that the field first passes through one medium and then through the other.

TABLE IV

Thermometer	1	2	3	4	5	6	7
Tempt. at start	12.0	12.0	12.0	12.5	14.8	16.2	17.0
Tempt. after 20 min. run	17.0	17.0	16.0	16.5	21.9	24.0	25.0
Diff. of tempt.	5.0	5.0	4.0	4.0	7.1	7.8	8.0
	← Gelatin →				← Lard →		

There are notably different temperature increases in the two substances, but the difference might be due to the lower specific heat of lard, as the result of which the same number of calories of heat generated in lard as in gelatine would produce a greater temperature rise in the lard. Again, it might be just simply due to a different rate of dissipation of short wave energy which causes the different heating in the two substances. The conditions are too

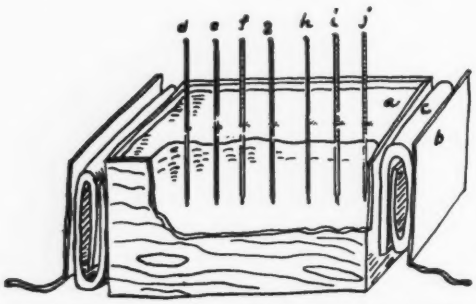

Fig. 2. The conditions of the first experiment with short wave therapy. The sketch illustrates a wooden box with part of the front broken away so as to reveal the gelatine contents with the thermometers in place. The electrodes are illustrated at the ends of the box with intervening padding: (*a*) gelatine in box; (*b*) electrodes; (*c*) padding; (*d*) to (*j*) thermometers.

complex to make a definite explanation possible.

Notably absent in these results is the greater extent of heating in the central regions. The reason for this is that a separation of the lard from the gelatine took place during the run and this caused some loss of heat and cooling in the center portion of the block. But heating resulted in both media as is to be expected on the basis that the field passes first through one medium and then through the other.

It is, therefore, shown by this experiment that if a fat layer is to be traversed by a short wave field that is in series with either muscle or bone, then there will be heating in this fat layer to a distinctly greater extent than in the muscle layers.

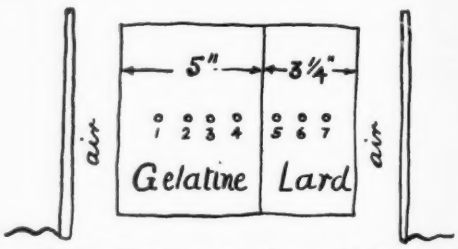

Fig. 3. Short wave experiment with lard and gelatine in series. The use and arrangement of blocks of lard and gelatine and also the position of the electrodes separated by an air space from the block are shown. The numbers from one to seven indicate the position of the thermometers with the size of the respective blocks in inches as marked.

V. In the arrangement shown in Figure 2, the gelatine and lard block was turned around so that the field traversed the two substances in parallel arrangement. The electrodes, which are air-spaced from the blocks, covered the end-portions of the two substances and, therefore, the same field was applied to both the gelatine and the lard block. Some of the thermometers were placed in the gelatine and some in the lard, as shown in Figure 3.

Striking is the fact, of course, that practically no heating took place in the lard. This is an indication that either the short wave length field is not absorbed appreciably in the lard or that the field was conducted very much better in the gelatine than in the lard. But Experiment IV shows that, if the short wave field is forced to pass through a substance such as lard, that heating takes place in it. Hence, in this experiment, the field, since no heating took place in the lard, must have been displaced and conducted better in the gelatine than in the lard.

TABLE V

Thermometer	1	2	3	4	5	6	7
Tempt. at start	15.8	16.3	16.2	18.6	20.2	21.0	21.3
Tempt. after 20 min. run	26.0	32.0	28.2	19.2	20.3	21.0	21.5
Diff. of tempt.	10.2	15.7	12.0	0.6	0.1	0.0	0.2
	← Gelatine →			← Lard →			

This deduction is in full agreement with the laws of field distribution in and around dielectrics (9). Therefore, it follows from

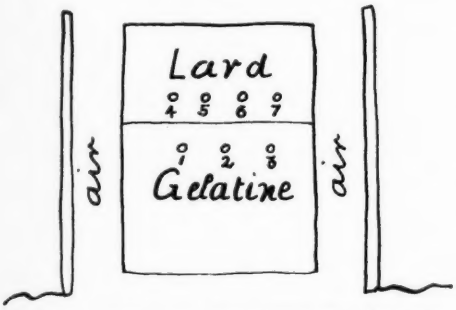

Fig. 4. Short wave experiment with fat and gelatine in parallel with the electrodes. In this experiment the lard and gelatin blocks were placed at right-angles to the position indicated in Figure 3. The position of the electrodes with intervening air spaces is as before. This arrangement of the thermometers is again indicated.

this experiment that the distribution of the heating in unlike substances is entirely different in the two cases of parallel or series traversing of different substances by short wave length fields.

DISCUSSION

Quite evidently, when contact is made between the electrodes and the medium to be treated, the current is conducted through the medium and the distribution of the lines of force in substances having different resistances is in accord with Ohm's law and heating is produced according to Joule's law, *i.e.*, dependent on RI^2.

Short wave length fields, if applied through air spaces between the electrodes and the medium to be treated, distribute according to the permeability of the interplaced media. If the medium is homogeneous in composition, the maximum temperature rise is in the center of the medium, and the air space, in the case of living patients, may contribute materially to this effect, due to surface cooling caused by the circulation of air.

In a heterogeneous medium, if two different media are placed parallel to the direction of the field, there is a distortion of the field and a more intensive concentration of it in the more permeable substance. If the two media are placed one above the other or in series grouping to the direction of the field, then the same field must pass through both media. A differential heating may take place, depending on the reaction of the medium to the field and on its specific heat.

It appears particularly indicated that attention be directed to those facts insofar as they pertain to the clinical treatment of patients having layers of adipose tissues located over layers of muscle tissue or bone. If the field is passing first through fat and then through muscle tissue, then there is likely to be more intensive heating in the fat, and it appears that a high temperature in muscle tissue cannot be produced without also developing a considerably higher temperature in the fatty layers.

But in the parallel arrangement of the media to the field, the fat layers are protected against overheating to the extent that any desired high temperature may be produced in the muscle layers without appreciably heating or injuring the fat layers.

SUMMARY

The experiments reported herein indicate that—

(1) The conductive contact of a dielectric substance between the electrodes and the patient gives rise to surface heating as well as heating of the dielectric. It also prevents a free circulating air space and surface evaporation.

(2) The most advantageous utilization of the characteristics of short wave therapy is accomplished when the electrodes are separated from the patient by an air space.

(3) With homogeneous parts to be treated, the maximum heating is in the middle of the part.

(4) With heterogeneous parts, if the parts are in series to the direction of the field, there is heating in all these parts but more in those having a lesser permeability; if the parts are in parallel to the direction of the field, there is greater heating in the part of greater permeability for the field.

(5) For patients' parts which are cov-

ered with fat layers, bones, or fluids and gases embedded in tissues, *i.e.*, whenever a distinct heterogeneity in regard to permeability to short wave field exists, in the series order of arrangement there is danger of overheating the less penetrable parts in relation to the heating produced in the more readily penetrated portions.

(6) In the treatment of deep-seated lesions by the combined short wave heating and radiation therapy method, the indicated procedure as applied by us is that the direction of roentgen irradiation would best be applied at right-angles to the field of short wave application, the electrodes being separated by an air space from the patient, with free air circulation and no interposition of insulating material. The time of application of short wave therapy should immediately precede and preferably continue through the time of roentgen exposure.

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THE END-RESULTS OF INJURIES TO THE EPIPHYSES[1]

By OSCAR LIPSCHULTZ, M.D., *Minneapolis*

From the Departments of Radiology of the University of Minnesota and the Minneapolis General Hospital, Minneapolis, Minnesota

THE purpose of this paper is to present the end-results in a group of traumatically displaced epiphyses. The work was prompted in answer to the oft-repeated question, "Does premature ossification or deformity result from such an injury?" Follow-up studies by means of roentgen examination were made from sixteen months to eight years after the injury.

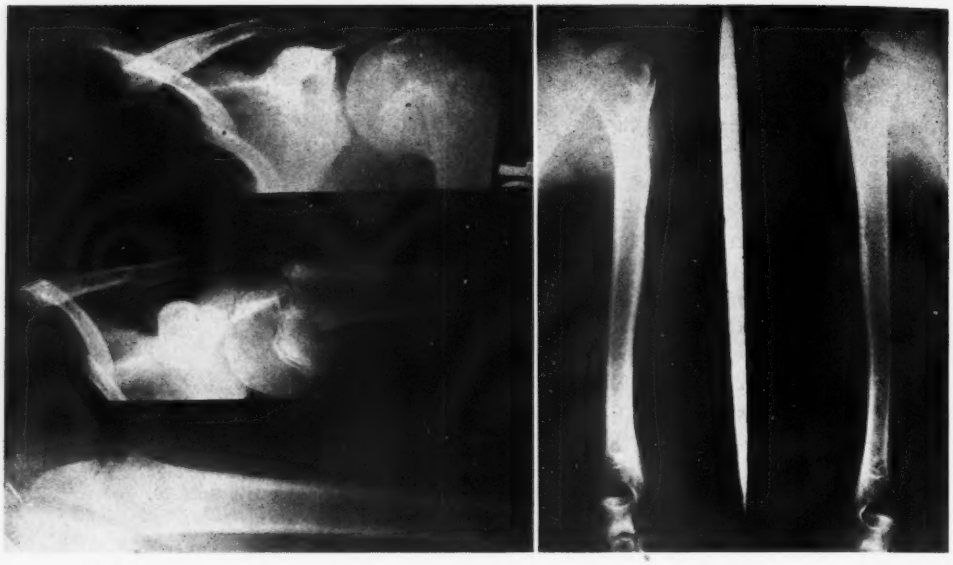
A review of the literature reveals relatively few articles which concern themselves with end-results subsequent to epiphyseal trauma. The conclusions of these papers are not in agreement. Eliason and Ferguson (1) have reported a series of 110 cases involving the epiphyses of various long bones of the body, from which they conclude that premature ossification occurs infrequently and that the degree of reduction is not a factor. Aitkin (2) has reported on 60 cases of displaced distal radial epiphyses and concludes that premature ossification with disturbance in growth occurs frequently but is usually insufficient to be of clinical importance. Compere (3) has reported a series of 19 cases in which the frequency of disturbed growth was 95 per cent; in a very high percentage this change in growth was of clinical significance.

The epiphysis is a secondary center of ossification the purpose of which is to promote bone growth. Its blood supply is practically independent of the shaft and is obtained from the periosteum. Only one or two small vessels pass from the shaft through the epiphyseal cartilage into the epiphysis. Ossification in the epiphyses and their union with the shaft occurs in a certain sequence. Those epiphyses which bear the largest relative proportion to the shafts to which they belong ossify first. Union with the shaft takes place first in those epiphyses toward which the nutrient vessel is directed. The epiphysis which is the last to appear is the first to unite. Growth takes place faster and for a longer period of time at the epiphysis which unites last. Since the nutrient vessels are directed toward the elbow and away from the knee, it is well known that growth takes place more rapidly about the knee, shoulder, and wrist. If injuries to the epiphyseal regions result in growth disturbances, then injuries to these areas should result in the more marked growth disturbances.

In this series of cases which we studied, re-examination of the injured as well as the uninjured member was made when possible. Roentgenograms of the limb in its entirety were made so that measurements of length could be accomplished and observations of deformity and premature ossification could be noted. The long bones of 33 presumably normal juveniles were examined and used as a basis of normal variation in bone length of one side of the body to the other. In this group of normals, we noted that in the radius there was a maximum variation of five millimeters. Most of the radii were either the same length or varied from one to two millimeters. These same variations held true for the ulna, tibia, and fibula. In the humerus there was a slightly greater normal variation. The difference in length amounted to as much as nine millimeters, with most of the humeri varying four millimeters.

In our files in the x-ray department from 1927 through 1933, we have records of 380 cases of traumatically displaced epiphyses (Table I). The epiphysis of the lower end of the radius was most frequently involved and accounts for 234, or practically three-fifths

[1] Presented at the Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Nov. 30–Dec. 4, 1936.



A *B*

Fig. 1. Patient is a boy, aged 12 years. Date of injury, July 28, 1933. *A*, Upper study is the first examination; middle study, the anteroposterior view after reduction; lower view, the lateral view after reduction. *B*, Injured side on the left, examined May 2, 1935. There is advanced ossification, with resulting shortening of the shaft of 25 mm. The uninjured side is on the right.

of all the cases. The lower epiphysis for the tibia was next in frequency and accounts for 59 of the cases. The upper epiphysis of the femur was not included in this series because of the difficulty in establishing trauma as the sole factor. Separation of the epiphyses of such long bones as the metacarpals or flat bones, such as the phalanges, were also excluded in this study. It will be noted that separation of some of the epiphyses about the elbow, such as the capitellum and trochlea of the humerus, the epiphysis for the head of the radius, and the epiphysis of the olecranon process of the ulna, did not occur in our series.

TABLE I.—DISTRIBUTION OF CASES OF TRAUMA TO EPIPHYSES FROM 1927 TO 1933

Epiphysis of lower end of radius	234
Epiphysis of lower end of ulna	15
Epiphysis of lower end of tibia	59
Epiphysis of lower end of fibula	4
Epiphysis of medial epicondyle of humerus	36
Epiphysis of lateral epicondyle of humerus	7
Epiphysis of upper end of humerus	18
Epiphysis of lesser trochanter of femur	4
Epiphysis of lower end of femur	3
	380

Follow-up studies from sixteen months to eight years later were possible in 106 cases, occurring in 100 individuals (Table II). In five of these cases there was a separation of the proximal epiphysis of the humerus in individuals between the ages of eleven and fifteen. In four of them there was an associated fracture of the adjoining diaphysis. In three of these four cases the degree of offset was not great enough to warrant reduction, while in the fourth case, there was a considerable offset which could not be completely reduced. The final study after reduction revealed a lateral displacement of the shaft through about one-half its width, with some overriding (Fig. 1). The study made twenty-

TABLE II.—DISTRIBUTION OF CASES WHICH WERE RE-EXAMINED

Epiphysis of lower end of radius	71
Epiphysis of lower end of ulna	5
Epiphysis of lower end of tibia	16
Epiphysis of lower end of fibula	2
Epiphysis of medial epicondyle	5
Epiphysis of lateral epicondyle	1
Epiphysis of upper end of humerus	5
Epiphysis of lesser trochanter of femur	1
	106

two months later revealed premature ossification, with a shortening of the humerus of 25 millimeters. In one case in which the epicondyle constitute the group of follow-up studies of epiphyseal injuries about the elbow. In two of these cases, one of each

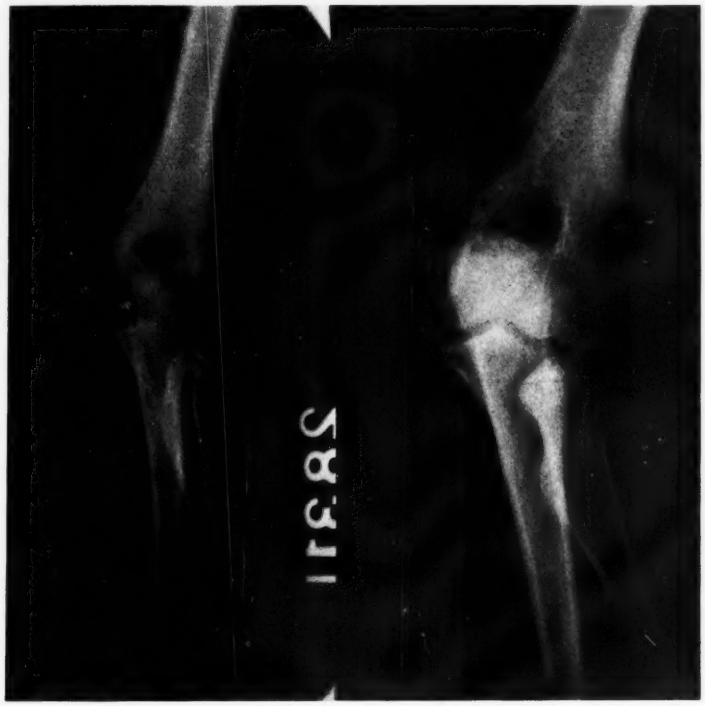


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Fig. 2. Patient is a girl, aged 11 years. Date of injury, May 2, 1929. *A*, Separation of the epiphysis of the medial epicondyle, with fracture of the neck of the radius. Elbow was immobilized with the alignment remaining the same. *B*, Roentgen study made Sept. 4, 1934. There is non-union of the epiphysis of the medial epicondyle and a deformity of the upper end of the radius.

offset was quite minimal, a follow-up study made twenty months later revealed premature ossification, with a shortening of the humerus of 16 millimeters. In both these cases of altered growth the cartilage on either side was very thin, so that it is very unlikely that there will be any appreciable further change when growth is completed. In the other three cases there was no interference with growth. Only one of these five cases was examined at the time of complete fusion of the epiphysis with the shaft.

Five cases of separation of the epiphysis of the medial epicondyle and one case of separation of the epiphysis for the lateral type, there was an associated dislocation at the elbow. Three of the separated epiphyses for the medial epicondyle underwent non-union (Fig. 2), while the other three epiphyses united. This group of injuries occurred in individuals from seven to sixteen years of age. Five of these cases were observed at the time of completed growth about the elbow.

Only one case of separation of the epiphysis of the lesser trochanter was reexamined. This injury occurred in a 14-year-old boy in whom reduction of the separation could not be accomplished. Reexamination five years later revealed that the epiphysis had united, leaving a very

definite deformity because of the excess bone production needed to fill in the area of separation (Fig. 3).

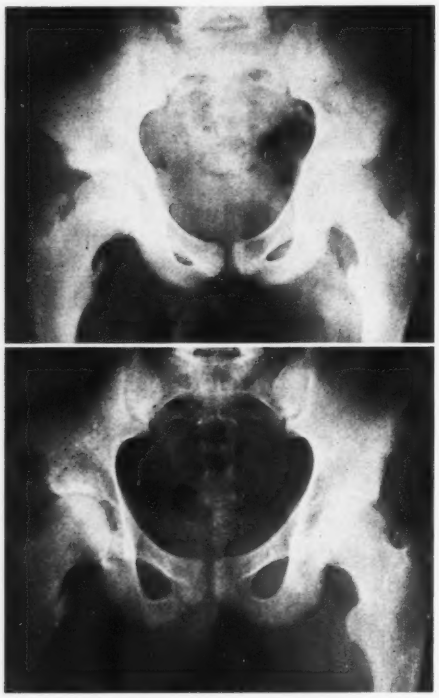


Fig. 3. Patient is a boy, aged 14 years. Date of injury, March 20, 1929; re-examination, Dec. 27, 1934. The upper figure reveals the separation of the epiphysis of the lesser trochanter on the left side. Reduction not possible. Lower figure reveals a resulting deformity five years later.

In injuries about the ankle, separation of the distal epiphysis of the tibia accounted for 16 of the re-examined cases. They occurred in a group of individuals ten to sixteen years of age. In all but two there was an associated fracture through the adjoining shaft; in four of the cases there was an associated fracture of the distal third of the shaft of the fibula. In two of these cases, there was a fracture through the epiphysis, with separation of only that portion of the epiphysis involved in the fracture. In one instance there was a slight separation of the distal epiphysis of the fibula. There was no interference with growth in any of these cases. In this group of ankle injuries there was also one case of separation of the distal fibular epiphysis, with minimal fracture of the adjoining shaft but with no other bony injuries about the ankle. Final film study in this instance revealed no evidence of disturbed growth. Five of this entire group of 18 epiphyseal separations were re-examined after complete fusion of the epiphysis with the shaft.

Re-examinations were made in 71 cases of displaced epiphysis which involved the lower end of the radius (Table III), in individuals who ranged from seven to seventeen years of age. In 56 of these cases, there was an associated fracture of the adjoining diaphysis. In 36 cases there was a fracture of the styloid process of the ulna; in four others, an associated fracture of the distal third of the shaft of the ulna. In three of these cases, there was a separation of the distal epiphysis of the ulna. Seventeen of these cases were observed at the time of completed growth. Roentgenographic evidence of growth change was noted in six instances, but none of them was of clinical significance (Table IV). In these six cases, the injured radius

TABLE III.—FINDINGS IN DISPLACEMENT OF DISTAL RADIAL EPIPHYSIS

Number of cases	71
Age of patients (years)	7–17
Number with fracture of shaft	56
Number with fracture of ulnar styloid	36
Number of cases with fracture of shaft of ulna	4
Number of cases with disturbance in growth	6
Number in which ulnar styloid did not unite	25
Number followed to complete ossification	17
Number with separation of epiphysis of ulna	3

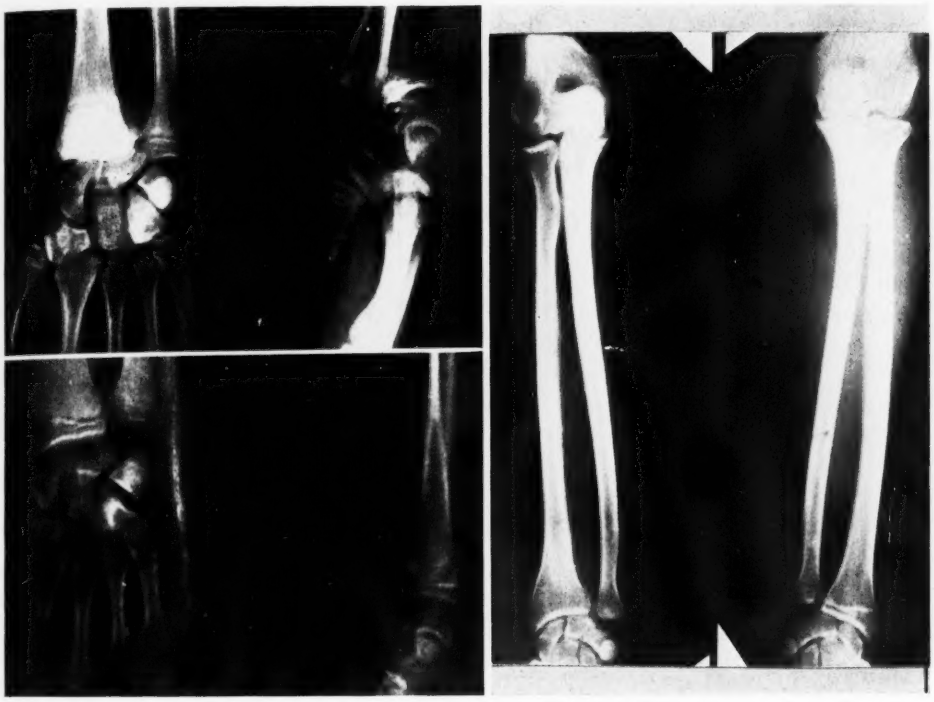
TABLE IV.—DISTRIBUTION RADIAL CASES WITH SHORTENING OF THE SHAFT

Age	Time Followed	Millimeters Shorter	Degree of Ossification
9	36 months	14	Normal
11	20 "	7	Normal
12	28 "	7	Normal
13	34 "	7	Advanced
15	24 "	15	Complete
15	36 "	16	Advanced

DISTRIBUTION OF ULNAR CASES WITH SHORTENING OF THE SHAFT

14	20 months	9	Advanced
15	65 "	14	Advanced
14	38 "	29	Advanced

was from seven to sixteen millimeters shorter than the uninjured; the ulna, as a consequence of this disturbed growth, became relatively longer on the injured than on the uninjured side. In none of these cases, however, was there enough disturbance in growth to permit the styloid process of the ulna to become as long or longer than that of the radius. In only two cases was there evidence of slightly greater ossification of the epiphysis; both of these occurred in individuals in whom the injured radius measured eight and sixteen millimeters shorter than the uninjured (Fig. 4). In the former case, growth was almost completed, whereas in the latter case growth was practically at an end. Only eleven of the 36 fractured ulnar styloids united.

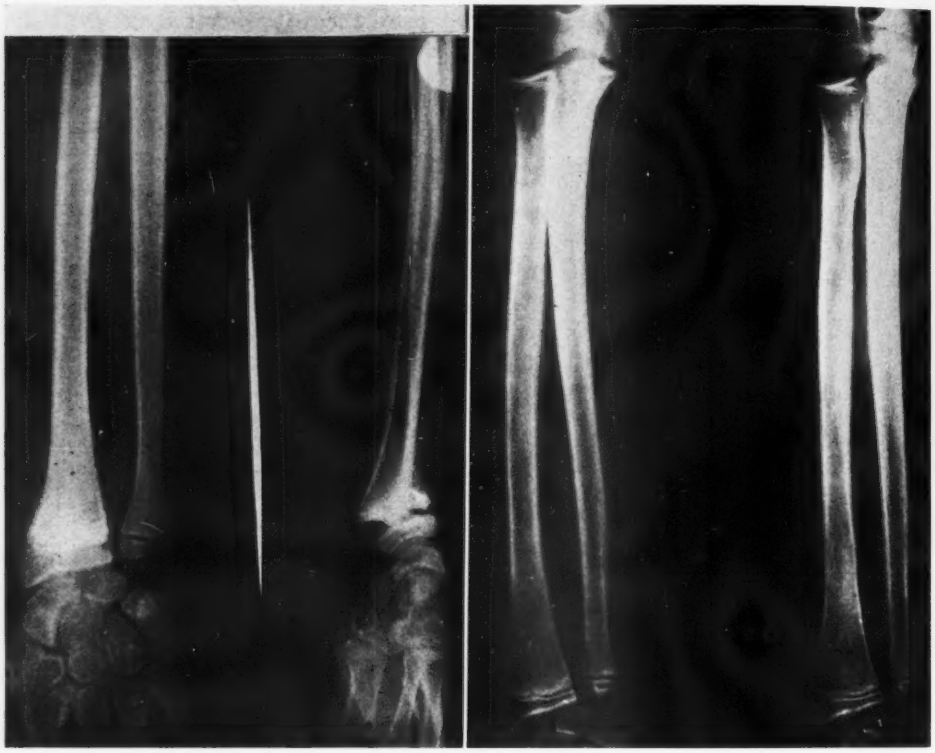


A B C

Fig. 4. Patient is a boy, aged 15 years. *A* (*upper left*) Lateral and anteroposterior views at first examination, May 27, 1932. Marked displacement of distal epiphysis of radius, with fracture of shaft. *B* (*lower left*) Study made after reduction. *C*, Forearm on left, injured side (May 31, 1935). Note advanced ossification in radius, which has become 16 mm. shorter than the normal one on the right. There is a resulting relative increase in the length of the ulna on the injured side as compared to the uninjured side.

In all the cases involving the lower end of the radius, reduction of the displaced epiphysis was attempted and usually accomplished in the first effort. In one instance a boy of thirteen came to the outpatient department two weeks after he had fallen off a parallel bar and injured his wrist (Fig. 5). He was sent to the x-ray department for study and was asked to return to the clinic on the following day. The x-ray examination revealed a posterior displacement of the distal epiphysis of the radius through one-half its depth, with tilting of the articular surface. Through some misunderstanding, the boy returned to the wrong clinic and, when an effort to rectify this mistake was made, he misunderstood these good intentions and finally gave up his original thought of

undergoing treatment. He carried his arm in a sling until it felt better and then began to use it. Follow-up study made twenty-four months later reveals no abnormality whatever about the injured radius, and it looked no different from the uninjured one. A somewhat similar experience as to what is considered inadequate treatment was encountered in the case of a seven-year-old boy who fell and sustained displacement of both distal radial epiphyses, which were subsequently replaced and immobilized. Film study made after the removal of the plaster thirty days later revealed that the epiphyses had slipped so that the one on the right was displaced posteriorly through slightly more than one-third the depth of the epiphysis, while the one on the left side had slipped to a slightly lesser degree. No further treatment was attempted. Films made sixty-five months later reveal no evidence of any growth disturbance.



A *B*

Fig. 5. Patient is a boy, aged 13 years. Injury occurred two weeks before the first study was made, Nov. 2, 1932. *A*, First examination. Note the marked displacement of the epiphysis of the radius, also the periosteal new bone along the posterior margin of the shaft. There is likewise a fracture of the styloid process of the ulna. No treatment was received in this case. *B*, Roentgen study made Nov. 5, 1934. Injured side on the right—normal growth. Uninjured side on the left.

In our series, we gathered five cases of separation of the distal epiphysis of the ulna. Three of these were in association with displacement of the distal epiphysis of the radius; the other two were in association with green-stick fractures of the distal third of the shaft of the radius. In three of these cases the epiphysis was displaced and carried with it a fractured fragment of the adjoining diaphysis, while the other two cases were characterized by fractures through the styloid process of the ulna which continued through the epiphysis

and the adjoining postero-lateral portion of the adjoining diaphysis. Reduction was accomplished in all of these cases

A *B*

Fig. 6. Patient is a boy, aged 13 years. Date of injury, Jan. 24, 1932. *A*, Anteroposterior and lateral views showing greenstick fracture of radius and fracture through the styloid process of the ulna, with fracture through the epiphysis and the postero-lateral margin of the adjoining shaft. There was no improvement on reduction. *B*, Re-examination on March 22, 1935. Roentgen study reveals a premature ossification of the lower end of the ulna, with a resulting shortening of the shaft of 29 millimeters. Note the ulnar bowing of the radius as a consequence.

except for the one in each group mentioned. In three of this small group of five cases there was a resulting premature ossification of the epiphysis, with resulting shortening of these ulnæ (Table IV). Two of these were in the first group mentioned in which the entire epiphysis was displaced; the third one occurred in the other group in the case in which reduction of the fracture was not accomplished (Fig. 6). In addition to the suppressed growth of these ulnæ, there was also an ulnar bowing of the radius, which was in proportion to the degree of shortening of the ulna. The resulting shortening ranged from nine to twenty-nine millimeters. These cases occurred in boys ranging from thirteen to fifteen years of age. Only two of these cases were observed at the time of completed growth, while in the others growth was almost complete.

It will be noted that in arrested growth of the ulna there is a resulting ulnar bowing of the radius which is proportional to the degree of suppressed growth in the ulna and, with this, there is an ulnar deviation of the wrist. If the deviation is not marked, this does not become of any clinical consequence, because the hand is normally strongest with the wrist in a state of ulnar deviation—the position assumed in heavy lifting or gripping. This tendency toward ulnar deviation of the radius in altered ulnar growth is best explained by assuming that, since in the use of the hand maximum strength is obtained with the wrist in a state of ulnar deviation, the tendency of ulnar bowing of the radius is normally present, but because of the splinting effect of the ulna this cannot take place during growth. In suppressed growth of the ulna during development this natural splint is removed and an ulnar bowing of the radius results. In arrested growth of the radius we have not

encountered in our work or noted elsewhere any radial bowing of the ulna. It would appear from the normal anatomy of the wrist that a certain amount of relative overgrowth of the ulna can be taken up by the soft tissue structures present between the lower end of the ulna and the triquetral bone. Until this space is taken by the relatively lengthened ulna there is no pressure on the triquetral to create a radial deviation of the wrist. When this does happen, radial deviation of the wrist supervenes but radial bowing of the ulna apparently does not take place because the wrist is then in a condition in which use of the hand is normally at its weakest—apparently not enough physical force can be mustered during development to cause radial bowing of the ulna even in the presence of an abnormally shortened radius.

SUMMARY

One hundred and six traumatically displaced epiphyses were observed for a period of time ranging from sixteen months to eight years following injury. Only a small percentage of these cases were seen less than two years later. This time interval is considered sufficiently long for growth disturbances to manifest themselves if they are to take place at all. In 15 cases there was x-ray evidence of premature ossification and suppression of growth (Table V). This group is made up of six radial cases in which there was retarded growth ranging from eight to sixteen millimeters; three cases in which the epiphysis for the medial epicondyle of the humerus failed to unite after separation; three cases in which there was premature ossification with shortening of the ulna; two cases which involved the proximal epiphysis of the humerus in a similar manner, and one case in which the separated epiphysis for the lesser trochanter of the femur united with deformity. In only three of these many re-examined cases was there noted a slight disturbance in function—cases of separation of the epiphysis of the medial epicondyle of the humerus which underwent non-union and resulted in a very slight limitation of extension. In all the other cases there was no limitation of motion.

CONCLUSIONS

1. Premature ossification, with changes in growth, takes place frequently after epiphyseal injury. It occurred in 15 cases in this series of 106 cases, or an incidence of 14 per cent.

2. The amount of shortening, however, is usually minimal and not of clinical significance.

3. Occasionally, however, we have a case in which the disturbance in growth is marked, resulting in deformity and disturbance in function. This occurs whether or not perfect reduction is obtained and is apparently due to trauma to the epiphysis itself at the time of the injury.

TABLE V.— DISTRIBUTION OF THE 15 CASES OF SUPPRESSED GROWTH OR DEFORMITY

	Epiphysis Involved	Resulting Abnormality
1.	Upper humerus	Premature ossification and 16 mm. shortening
2.	Upper humerus	Premature ossification and 25 mm. shortening
3.	Medial epicondyle humerus	Non-union
4.	" " "	"
5.	" " "	"
6.	Lower radius	7 mm. shortening
7.	" "	7 mm. shortening
8.	" "	8 mm. shortening with advanced ossification
9.	" "	14 mm. shortening with advanced ossification
10.	" "	15 mm. shortening
11.	" "	16 mm. shortening with advanced ossification
12.	Lower ulna	9 mm. shortening with advanced ossification and of radius bowing
13.	" "	14 mm. shortening with advanced ossification and of radius bowing
14.	" "	29 mm. shortening with advanced ossification and of radius bowing
15.	Lesser trochanter of femur	Deformity

4. Perfect reduction should be attempted, but may not be necessary in the treatment of the traumatically displaced epiphysis.

5. Osteotomy in neglected cases in the young is probably not necessary, since the deformity does not persist.

6. In disturbed ulnar growth, ulnar bowing of the radius supervenes and, if very pronounced, produces disturbed function.

7. In disturbed radial growth, radial bowing of the ulna does not result. Disturbed function results only from the more marked growth disturbances.

The author wishes to thank Dr. K. E. Fritzell, of the surgical staff, for his help.

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DISCUSSION

DR. LEO G. RIGLER (Minneapolis): Anyone who has practised roentgen diagnosis for a long period of time has either been asked or has asked himself the question over and over again, when he sees these cases of displaced epiphyses, as to what the end-results will be.

I think there has been in the back of our minds, at least, a considerable fear in every case in which we see a rather marked displacement of the epiphysis that a serious deformity may result because of the disturbance in growth which ought to occur. One would think it ought to occur.

If you consult textbooks for this answer, I think you will find that they uniformly evade it and that there is little or nothing to give you an intelligent concept of the end-result. It is for this reason that Dr. Lipschultz entered into this study in the hope of being able to give a more adequate answer than had previously been given.

I think, on the whole, the results of his work would indicate that no great fear should be felt—that the end-results of traumatic injury to the epiphysis are not very serious in the vast majority of cases.

Incidentally, he finds that the degree of reduction apparently is not an important factor, and I should like to emphasize again the one case he showed in which no reduction was attempted, in which perfect results occurred. There have been other cases of similar nature reported in the literature.

I might say parenthetically that because of lack of time, he did not show all the films on these cases. The question might arise, for example, as to what the lateral view showed in that particular case he demonstrated, and I can assure you that there was no deformity whatsoever visible in the lateral as well as in the anteroposterior view.

I think, however, we should not be misled by this result into thinking that infectious lesions at the epiphyseal line, or other types of non-traumatic injury, would have the same result. Many years ago Huenekens and I reported a case of osteo-myelitis variolosa the osteomyelitis of smallpox, in which multiple abscesses occurred in the epiphyseal zone itself. This was in a child; a most extreme and serious deformity resulted because of the fact that growth was promptly stopped after a few months, —and because, again, only one bone of the forearm or of the leg was involved, a marked deviation of the extremity occurred, with a marked disturbance of function.

Similarly, the late Harry Hillstrom in our department studied the effects of irradiation on the growing bones. He irradiated the epiphyses and epiphyseal lines in animals during the period of growth, and found that with a sufficient amount of irradiation, most serious disturbances in growth may occur.

Bisgard has recently done similar work and has shown much the same result—

that one can produce a complete stoppage of growth in a long bone as a result of irradiation, with, of course, the resultant deformity that one might expect.

I think it is important, however, to realize that in the vast majority of these cases of traumatic injuries, very likely no untoward results will occur.

CASE REPORTS AND NEW DEVICES

BILOBED GALL BLADDER
(VESICA FELLEA DIVISA)

By LAWRENCE M. HILT, M.D.,
Roentgenologist, St. John's Hospital, *Springfield, Ill.*[1]

Anomalies of the gall bladder in the human being are rare. We are indebted to Boyden (1), who has made an extensive study of the gall bladder in both animals and man. Recently Gross (2) published a very comprehensive article listing six cases of bilobed gall bladder which he was able to find in the literature, only one of which was diagnosed by cholecystography. An additional case that was recognized by the above procedure and confirmed at operation is submitted.

The roentgenologist should be familiar with these malformations in order that an unusual shadow of the gall bladder may be correctly interpreted. With the increasing use of cholecystography, it is probable that these anomalies will be found with greater frequency. Boyden found cats had bilobed gall bladders in about 10 per cent of the total number he examined.

Fig. 1. Four-hour film.

Embryologically, a bilobed fundus is explained as follows: The single bud becomes paired, but a primary connection is maintained, thus forming two separate and distinct fundi with a single cystic duct. In two of the previously reported cases, the external appearance of the gall bladder showed quite a longitudinal septum. In the others and our own case, there are two separate cavities.

The clinical evidence is not characteristic of an anomaly.

CASE HISTORY

Female patient, aged 37 years, complained of a pain in the abdomen, with no particular relation to type of food or time of eating. There was no history of vomiting, or jaundice. She had lost about thirteen pounds in weight in six months' time. Physical examination was normal, except for tenderness on palpation of the abdomen, particularly on the right side. The pain seemed to radiate equally in all directions. Blood count was within normal limits. Gastric analysis at the end of fifty minutes gave 25° free hydrochloric and a total acidity of 45°. Occult blood, lactic acid, and microscopic examinations were negative.

Roentgenoscopic and radiographic examinations of the gastro-intestinal tract revealed no abnormalities. A plain film of the gall-bladder area showed no demonstrable pathology. The gall-bladder dye was given intravenously, radiographic observation being made at four and six hours and one hour after a fat meal.

Fig. 2. Six-hour film.

The interpretation of the films was as follows: "The gall-bladder shadow can be definitely outlined four hours after the intravenous administration of the gall-bladder dye. The gall bladder appears to be divided into two parts. This is further visible at the end of six

[1] Now Roentgenologist, Butterworth Hospital, Grand Rapids, Mich.

hours. One hour after the fat meal, this division of the gall-bladder shadow can be more clearly outlined, the gall bladder having emptied itself over 80 per cent. The diagnosis arrived at is bilobed gall bladder."

Fig. 3. One-hour after fat meal.

At operation a bilobed gall bladder, with one cystic duct, was found. A partial cholecystectomy was done. The appendix was removed. Pelvic examination at operation revealed no evidence of pathology. The abdomen was closed, with a cigarette drain in place. The patient made an uneventful recovery, with relief of the previous complaints.

The gross and microscopic descriptions of the gall bladder, as reported by Dr. F. W. Light, pathologist, are as follows:

Gross Examination.—The specimen is the distal two-thirds of a gall bladder. It has an unusual shape, the fundus being divided into two lobes of about equal size. Collapsed, the specimen measures 4 × 3.5 × 1 cm., and weighs 6.5 grams; most of its external surface is smooth and it has a deep pink color. The gall-bladder wall is fairly thin and pliable; the mucosa is reddish-brown in color; no stone is present.

Microscopic Examination.—The sections are taken from the edge of the specimen, and include parts of the proximal portions of both lobes of the fundus. There is present a rather thick layer of subserosal fibrous tissue. The muscularis is broad and shows interstitial fibrosis. The mucosa is considerably flattened out, the epithelium being well preserved. Scattered through the muscularis are a few narrow sinuses lined by epithelium.

There is, thus, chronic inflammation, as well as an anatomical anomaly of the gall bladder. The appendix is normal.

Grateful appreciation is hereby expressed to Dr. C. W. Compton for the clinical data and operative details of this case.

SUMMARY

1. Bilobed gall bladders in the human are rare.
2. Careful study of roentgenograms may reveal the true nature of this lesion prior to operation or postmortem.
3. An additional case is added to those previously reported.

Fig. 4. Gross specimen.

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A CHEST CRADLE FOR THE ROENTGEN EXAMINATION OF THE FEMALE BREAST

By J. GERSHON-COHEN, M.D.
Philadelphia

The possibilities of studying mammary disease roentgenographically seems very promising. To overcome some of the technical difficulties involved in making roentgenographic examinations of the female breast, a chest cradle was devised so that duplicate roentgenograms could be obtained, standardizing the technic and making possible the study of growth of any tumor or the effect of any form of medical or radiologic therapy.

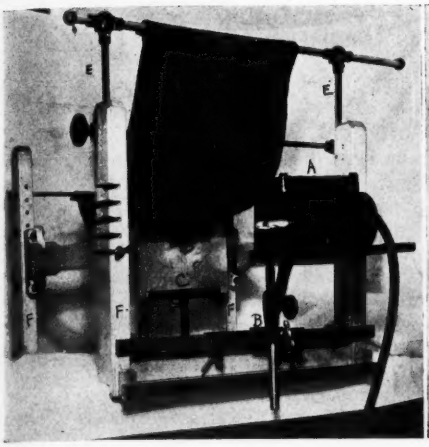

Fig. 1

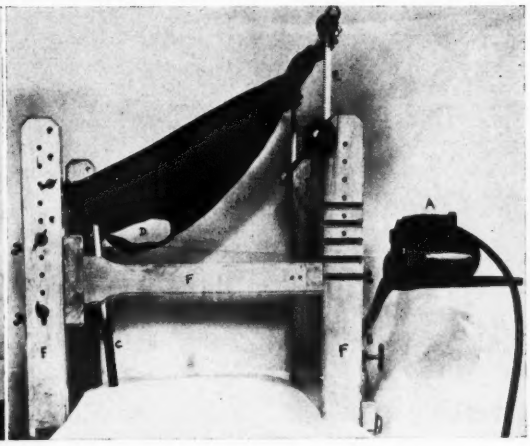

Fig. 2

Figs. 1 and 2. (*a*) Shockproof oil-immersed x-ray tube; (*b*) mounting and carriage for the x-ray tube; (*c*) plate holder with a telescopic arm; (*d*) opening in canvas sling; (*e*) notched arms bearing cross piece to which one edge of suspension canvas is attached making possible the elevation of one side of torso so that a view of the opposite breast is clear; (*f*) supporting posts.

Fig. 3.

Fig. 4.

Fig. 3. A roentgenogram of a mammary gland made with the old technic, showing a growth in the upper region of the breast, found by the pathologist to be a scirrhous carcinoma.

Fig. 4. The same breast as examined with the use of the chest cradle, showing the growth in its more natural architectural relationship to the whole mammary gland, two irregularly outlined cords of infiltration being prominently visible in the upper portion of the breast.

The apparatus consists of four posts which can be made of any material that is sufficiently rigid to bear the weight of the heaviest person on a canvas sling suspended from crossbars. One of these crossbars itself is attached to vertical supports which are movable in ratched grooves in two of the posts so that elevation of one edge of the canvas sling is possible when desired.

Fig. 5. Patient in position to be examined, resting on knees, body suspended prone on canvas hammock with breast hanging vertically through opening; the other breast is rotated upward, as the side of the patient's body is elevated opposite to that to be examined, removing all interference with the projection of the beam of x-rays.

By raising the edge of the canvas opposite to the side of the breast that is to be examined, interference with the horizontal central beam of x-rays is avoided as it traverses the breast tangentially to the chest wall. While diverse methods can be adapted for placing the film in position, we simply use a stand with a telescopic plate holder devise which can be placed in position and elevated to the desired height, being necessarily changeable with different sized breasts. A plate tunnel can be used when stereoscopic films are desired. A light shockproof, fine focus, portable x-ray head and tube is used as our source of x-rays and this is supported on a carriage attached to a cross member, movable in both the horizontal and vertical planes so that the central ray can be directed along any desired line.

NON-TRAUMATIC DILATATION OF THE UTERINE CERVICAL CANAL

By W. H. McGUFFIN, M.D., *Calgary, Alberta, Canada*

In an article entitled "Technic of Radium Treatment of Cervical Cancer," Dr. Frank E. Simpson, of Chicago,[1] advocated a method whereby the least possible irritation to the malignant tissues would ensue. I was keenly impressed but as I did not have available a supply of radium emanation or radium cells which could be utilized in a small caliber flexible lead applicator, some substitute method had to be devised.

After a search an economic and highly efficient non-traumatic cervical canal dilator was discovered, or maybe I should say re-discovered. This dilator (Fig. 1) is known as "The Sea-tangle Tent Dilator,"[2] but at the Radium and X-ray Institute in Calgary, it is known as "The McGuffin Dilator."

"The Sea-tangle Tent Dilator" has been found to be of value because:

(1) There is no pain to the patient.

(2) No analgesic or anesthetic is necessary for its introduction.

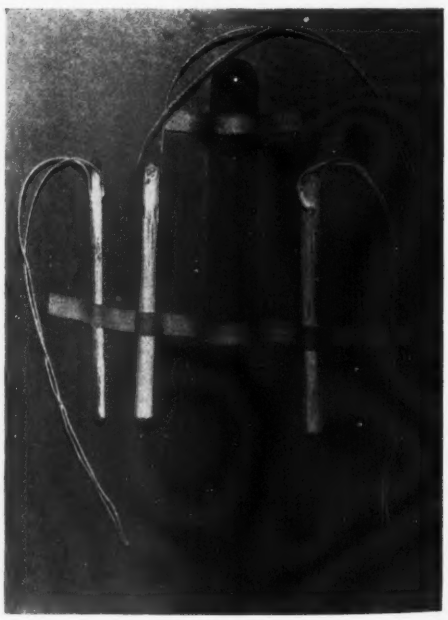

Fig. 1

[1] Am. Jour. Roentgenol. and Rad. Ther., Vol. **27**, 775.

[2] Procurable from the American Specialties Co., Inc., 131 E. 23d St., New York, or from Ingram & Bell, Ltd., Toronto, Canada.

(3) No instrumentation, no grasping of the cervical tissues with a tenaculum, or forceful dilatation with metal dilators.

(4) The dilator is easy to sterilize; in fact, the manufacturers are now supplying the dilator in sterile oil enclosed in a hermetically sealed glass tube.

(5) The dilator is supplied in various sizes, so that a dilator of the proper size may be selected.

(6) Easy introduction.

(7) No bleeding, because there is no bruising of the tissues.

(8) No dissemination of malignant cells, because there is no trauma.

TECHNIC FOR USING "THE SEA-TANGLE TENT" DILATOR

(1) Patient is prepared as for a surgical dilatation and curettage.

(2) Patient is placed in the lithotomy or knee-chest position.

(3) Speculum is introduced into the vagina. Tissues of the cervix and vaginal vault are cleansed by the application of swabs using 1:2500 metaphen solution.

(4) A flexible uterine sound is passed to determine the length and direction of the uterine canal. This is the only instrumentation and is necessary for the determination of the linear dimension of the uterine canal in order that the technician may prepare the radium applicator with the proper number of radium centers, and, if necessary, an angulator to secure easy non-traumatic introduction of the radium applicator.

(5) The size of the external os is determined and the proper size of dilator is selected; that is, one which can be passed into the canal easily.

(6) The sterilized dilator is then soaked in 1:2500 metaphen solution for a few minutes until it is soft enough to be pliable.

(7) The pliable dilator has a long string threaded at one end. A pair of long handled forceps take hold of the string end of the dilator and, under good light, the dilator is passed into the cervical canal without force.

(8) The vagina is now tightly packed with sterile gauze strips, which are left in place for 24 hours.

(9) The radiotherapist then removes the packing and the dilator. It is interesting to notice the size of the dilator at this time. It has increased in caliber at least three or four times. The tissues are now swabbed clean and the radium application made immediately.

THE MOST ADVANTAGEOUS TIME TO USE THE SEA-TANGLE TENT DILATOR

(1) When the external os can be distinctly seen.

(2) Only after thorough preparation of the parts as for surgical procedure.

(3) When immediate radium application to the intra-uterine tissues is planned. The dilator is not to be removed until radium application is to be made; that is, approximately 24 hours after the introduction of the dilator. If the canal is not sufficiently dilated to take the radium applicator, then it would be advisable to use a larger dilator and wait a further 24 hours before making the radium application. It is not advisable to remove the dilator at the end of 24 hours and then to wait for 48 or 72 hours before administering the radium, because there is a tendency for the uterine canal to contract considerably after the dilatation process.

(4) At the time of biopsy. It has been the experience of those making intra-uterine radium applications that certain types of biopsy section procedure so mutilate the cervical tissues in the region of the cervical canal that when the radium treatment time arrives the external os is obscured, or the canal distorted. Either of these two factors handicap the successful intra-uterine radium treatment. If at the time of the biopsy, the external os can be visualized, it would appear that this is the best time to use the dilator. Should the planned treatment call for external irradiation before the local radium application, then it will be necessary to repeat the dilatation procedure immediately before the introduction of the intra-uterine radium applicator.

(5) In case there is a large fungating mass or deep crater ulcer at the site of the cervix, it will be impossible to use the dilator because the external os will not be visible. It will be necessary to wait until these conditions have been so altered by local or external irradiation, or following the removal of the overgrowth tissue by electrothermic methods, that the opening into the cervical canal is patent before attempting to introduce the dilator.

CONTRA-INDICATIONS

(1) Severe infections which would prohibit immediate intra-uterine irradiation.

(2) Thick cicatricial tissue encroachment upon the cervical canal, as exemplified by the following case:

The dilator had been introduced into the cervical canal and 24 hours later I attempted to remove it. The dilator seemed to fit the canal very snugly and did not budge upon the gentle traction usually made upon the string attachment. Mental perturbation was experienced and I had visions of necessary surgical procedure. The dilator had become greatly swollen but was soft, so by a slow-motion, unscrewing procedure, the pessary was delivered with

satisfaction to all. It had been fixed within the canal by a circular constriction. This is one case probably in which forceful graduated dilatation by the use of metal dilators might have been advantageous, but such occurrences must be extremely rare. The outcome was favorable and the radium application was made without further interruption.

SUMMARY

(1) An economical and painless cervical canal dilator is brought to your attention.

(2) A technic for dilatation of the cervical canal is described which is non-traumatic.

(3) The method is practical as proven by me during several years of daily utilization.

224 7th Ave. West

A RADIOGRAPHIC DEVICE FOR THE ANTEROPOSTERIOR MENSURATION OF THE ETHMOIDS AND SPHENOIDS

By S. FINEMAN, M.D., M.A., *New York City*

Accurate information regarding the posterior extent of the ethmoids and sphenoids may be of considerable clinical importance to the rhinologist in the medical or surgical treatment of these sinuses. To the best of the writer's knowledge, radiographic mensuration of these sinuses is not being practised to-day.

The method here proposed is based on the well-known radiographic principle, that an object placed in the same plane as the part radiographed will be magnified on the roentgenogram in the same relative degree as the part under examination.

Figures 1, 2, and 3 illustrate a measuring device and the resulting roentgenogram. The ruler, as shown in these illustrations, is cut from a piece of one-sixteenth or one-eighth inch of lead and is notched in centimeters. This lead ruler is then tacked on to a strip of wood, which, in turn, is tacked on to another narrow strip of one-sixteenth inch lead at right-angles to the ruler. This second strip of lead is inserted at the upper end into the clamp of a head mirror band, as shown in Figure 2. The end of the lead strip is shaped around a small ball bearing, so that it can be grasped firmly by the clamping device of the head mirror band.

The lower end of the lead strip can be shaped to fit under the patient's chin, where it can be held in place by a strip of adhesive plaster (Fig. 2).

Before adjusting this measuring device to the patient's head, nose, and chin, a narrow and thin strip of lead is molded to the patient's nose and is held in place with a strip of adhesive plaster. This is for the purpose of outlining the profile of the nose on the roentgenogram (Fig. 3).

The sinus roentgenogram can then be made with the patient in the sitting or horizontal position. In either case it is important to

Fig. 1. Shows the lead ruler measuring device adjusted in the mid-sagittal plane of the head.
Fig. 2. Shows a profile view of the head with the lead ruler in position, and the strip of lead molded to the nose.

adjust the patient's head and lead ruler so that the thin edge of the ruler coincides with the mid-sagittal plane of the skull, and so that both the mid-sagittal plane of the skull and flat surface of the ruler are parallel with the film. This avoids distortion of the ruler and of the skull structures on the roentgenogram and assures similar enlargement of the ruler and of the cranial structures which lie in the mid-sagittal plane of the skull. If the roentgenogram is made with the patient in the upright position, the weight of the device is sufficient to maintain its position in the mid-sagittal plane. In the horizontal position, small blocks of wood of suitable height can be used to support the lower end of the ruler at the proper level.

After the roentgenogram is obtained the determination of the anteroposterior depth of the ethmoids or sphenoids is carried out as follows: A celluloid ruler is placed on the roentgenogram so that it extends from the tip of the nose to the sinus to be measured. The distance between these two points is noted. The celluloid ruler is then superimposed over the shadow of the lead ruler on the roentgenogram, on which this distance is read off directly in centimeters or fractions of a centimeter, as shown by the magnified centimeters on the lead ruler.

Fig. 3. Shows the roentgenogram of the skull with the ruler in position, and lead strip over the nose. The centimeters on the lead ruler and the cranial structures in the mid-sagittal plane of the skull show practically the same magnification.

For clinical purposes the ethmoid cells and sphenoids can be considered as lying practically in the mid-sagittal plane of the skull. The magnification of these structures on the roentgenogram is within practical limits, the same as the magnification of the lead ruler.

133 East 58th Street

EDITORIAL

LEON J. MENVILLE, M.D., *Editor* HOWARD P. DOUB, M.D., *Associate Editor*

GROUP HOSPITALIZATION INSURANCE

THE STATUS OF RADIOLOGISTS IN RELATION TO THIS TYPE OF HOSPITAL PRACTICE

The majority of physicians in this country are well aware that one of the major problems facing them to-day is the attempted inclusion of the professional services of some of them in and as a part of the hospital benefits of group hospitalization plans. The services of radiologists have been included in the group hospitalization insurance plans of Cleveland for some three years and of New York for some two years. Since these hospitalization insurance plans are under lay control and since corporations cannot practise medicine, the implication is that radiology is a hospital and not a medical procedure. Fortunately, in most communities, the weight of opinion of the organized medical profession has been sufficient to persuade persons interested to exclude radiology and other forms of medical practice from these plans. In this connection, it is noteworthy that the first and oldest successful group hospitalization plan, namely, the Baylor Plan, never has had radiology amongst its benefits.

Within recent months there have been two encouraging developments. The first of these is the establishment of the Alameda County Group Hospitalization Plan, wherein radiology is provided to subscribers, but is provided on a legal and ethical basis. In this plan the Association indemnifies the subscriber to pay his radiologist for such services as are necessary while the subscriber is hospitalized. In this manner the patient personally pays the physician (that is, the radiologist) who provides the x-ray services, thereby complying with the law, and helping indirectly to uphold the status of radiology. Secondly, the Group Hospitalization Plan of Memphis, which formerly included discounts for x-ray work, now excludes such as being contrary to the ethics of the American Medical Association and contrary to sound medical practice. This revision was secured by the constructive co-operative efforts of the local county medical society.

These facts are being brought to the attention of all the members of the Radiological Society of North America, and especially to the members resident in New York City and Cleveland. We believe that the Counselors of these two districts should bring these important developments to the attention of all radiologists in their respective districts to the end that the various county medical societies located therein be notified. Following this notification, the Executive Committees of those county medical societies should be requested to approach the hospital authorities to the end that the existing evil situation be corrected. The exact wording of the Alameda County Medical Society Hospitalization Policy can be secured by writing the Secretary, care of the Samuel Merritt Hospital, Oakland, California; the details of the Memphis Hospitalization Policy revision can be secured from the Secretary, the Shelby County Medical Society, Memphis, Tennessee.

L. HENRY GARLAND, M.D.

COMMUNICATIONS

Nov. 30, 1936

Dr. E. J. Bertin,
Philadelphia, Pa.

Dear Doctor Bertin:

The phenomenon described as "pneumothorax in the newborn" [1] has undoubtedly been observed by numerous radiologists, who, as myself, have not considered it to be of such etiology. Upon first consideration, the interpretation seems to be that of minimal pneumothorax, but the perplexing incongruity of a history of normal delivery, no attendant dyspnea or cyanosis, or other respiratory embarrassment, and an absence of physical signs are mainly instrumental in the reluctance to diagnose this "sign" as unqualifiedly due to pneumothorax. Many of the cases encountered by the writer were observed in the routine

[1] Paper entitled Pneumothorax in the Newborn, by E. J. Bertin, RADIOLOGY, November, 1936, **27**, 584.

chest examination for so-termed enlarged thymus. It is not my intent to question the diagnosis of pneumothorax in most of the cases reported, but merely to determine whether the mere existence of a peripheral pulmonic strip of radiolucency could not be simulated by other conditions, in lieu of pneumothorax. Since this sign is not an infrequent finding, is it not possible, or probable, that whenever incomplete inflation of the lungs of the newborn occurs, this appearance might be present; and under certain circumstances be somewhat different in roentgen appearance from true atelectasis? The *modus operandi* could be deficient thoracic contraction, with relatively greater diminution in size of pulmonic structure, causing an exaggeration in width of the normal potential pleural space. Again, the converse might apply, namely, incomplete expansion of the lungs. The rather high incidence of this phenomenon, and particularly its bilateral appearance, seems rather incredible if resultant of ruptured pleura and spontaneous pneumothorax. This is especially true in cases presenting no symptoms or signs. Since other serous cavities, *viz.*, articular space of knee and shoulder, have been roentgenographically demonstrated without injection of air, under ideal conditions, is it not possible that this appearance in the newborn is visualized pleural space without introduction of air, its demonstration being enhanced by narrow chest, incomplete expansion of lungs, and coincidental exposure made at the extreme expiratory phase of respiration, as is frequently the case with the infant crying? The frequent association of strangulation by the umbilical cord, as reported by another author, would certainly suggest an etiologic factor of incomplete rather than excessive pulmonic expansion, with pleural rupture and ensuing pneumothorax. Of some seeming import is the fact that there is more frequent and greater involvement of the right side, although bilateral involvement is common. This might be explained upon the basis of insufflation of mucus, etc., into the bronchial tree, and due to the unique angulation of the carina, more frequently to the right side; which mechanical factor might also be ascribed to the rather common practice of placing infants upon their right side. Both promulgations favor the incomplete pulmonic expansion theorem.

The association of pleural exudate and pneumothorax is common, which, however, has not been demonstrated in the paper or noted by myself. As explained in your paper, the roentgenograms are not customarily obtained with the infant in the erect position and a minimal amount of free pleural fluid might readily be overlooked or masked in the recumbent posture. Further studies with the examination made in the erect position may clarify this discrepancy. The infrequency of pleural infection, assuming the pneumothorax etiology, is not evidence pro or con; for the paucity of bacterial invasion of the lungs at this age is notable. In some of the cases presented, and in the writer's own experience, no classical roentgenographic signs of pneumothorax were definable; but again, this could be explained in the counterbalance of slightly increased intrapleural pressure, and opposing elastic recoil of the pulmonic structure. It might be added that, in certain instances, an inordinately rapid disappearance of this phenomenon occurred, which seems incompatible with absorption of pleural air.

In concluding, further study of this interesting phenomenon will attest to the validity of this sign as pathognomonic of pneumothorax, or demonstrate whether other factors might simulate this appearance. I wish to compliment you, Dr. Bertin, on your excellent presentation, and to concur with you in regard to the alleged artefact as productive of this sign.

With kindest regards,
Sincerely,
WILLIAM R. STECHER, M.D.

January 6, 1937

Dr. William R. Stecher,
Easton, Pa.

Dear Doctor Stecher:

I want to thank you for the very thorough discussion of my paper on "Pneumothorax in the Newborn," which I presented to the Radiological Society.

In that discussion you offered as an objection to the occurrence of pneumothorax, the fact that several of the cases occurred after "normal delivery." I am satisfied that under certain conditions there is sufficient pressure and force exerted on the fetus during many so-called "normal deliveries" to rupture an alveolus after air has entered the lungs, especially in the presence of obstruction in the pharynx, larynx, or bronchus, even though the obstruction be only temporary. The pressure exerted during active labor has been estimated by

various authorities as being between thirty and sixty pounds per square inch of surface.

The degree of cyanosis or other evidences of respiratory embarrassment would naturally be dependent upon the amount of air in the pleural cavity, and upon the presence or absence of displacement of the heart and mediastinal structures. We have seen this beautifully illustrated on numerous occasions in adults with pneumothorax.

I cannot subscribe to your explanation of the appearances obtained in our cases as being due to an exaggeration in the width of the normal potential pleural space. If we admit of the presence of a demonstrable space, we should not refer to it as being potential. I am sure that the cases which we presented did not confuse potential with actual pleural spaces, and if the chest failed to contract as you suggest, I am sure that the lung and visceral pleura could not recede from the chest and parietal pleura unless some substance (such as air in our cases) entered the pleural cavity. One gets the impression from your explanation that a vacuum occurs in the pleural cavity, which, of course, is quite impossible. Before birth and in the stillborn there is no visible pleural space. This, then, is a true potential pleural cavity and is kept so by contraction of the chest wall and elevation of the diaphragm, and remains in this condition until some substance, such as air, finds its way between the two pleural layers.

Our cases illustrate an actual and not a potential pleural space. I feel sure that after consideration of these few remarks, and a review of your discussion, you will see how inadequately you explain the phenomenon and appearances which we illustrated in the seven cases presented in our paper.

Let me again thank you for your lengthy and interesting discussion. Hoping that some keenly observing obstetrician may detect definitely the manner in which this fascinating, if not important, condition is produced, by careful observation of the newborn during and immediately after even so-called "normal deliveries," I remain,

Very truly yours,
E. J. BERTIN, M.D.

DISCUSSION[1]

DR. PHILIP J. HODES (Philadelphia): The importance of this subject is self-evident and we feel that Dr. Bertin has done justice to it. One pitfall in diagnosis of pneumothorax in the newborn child merits further discussion.

Sometimes in holding the child for chest examination, the skin on the chest may be accidentally folded on itself. The roentgen manifestation of this artefact has been confused with pneumothorax. In order to satisfy ourselves that folds of the skin could simulate pneumothorax roentgenographically, we made roentgenograms of the chest of healthy infants. Following these routine exposures, the skin was deliberately folded and roentgen changes similar to those of pneumothorax were produced.

While pneumothorax in newborns undoubedly does occur, the possibility of this artefact as a source of error must, consequently, be kept in mind.

DR. E. J. BERTIN (closing): I agree with you that caution must be used in making a diagnosis of pneumothorax. You have pointed out and illustrated with lantern slides, an appearance which might possibly be mistaken for pneumothorax, but on close inspection definite evidence of pressure effect could be seen. Either the outline of the upper arm or the fingers of a nurse or assistant were clearly visible in your illustrations.

We also have seen these pressure effects many times, not only in infants, but also in children and adults, but we have had little or no difficulty in recognizing them, especially because both of these structures contain bone. Besides, the convexity of the pleural margin in pneumothorax as contrasted with the straight or concave outline with the arm or fingers present, renders the differentiation quite easy. We made numerous films after folding the skin in various areas on the front and back of the chests of infants, fixing the folds with adhesive plaster, but the appearances obtained could not be confused with those illustrated by our cases.

[1] Discussion of Dr. Bertin's paper after its reading at the Cincinnati meeting.

TEXAS RADIOLOGICAL SOCIETY

The Twenty-fourth Annual Meeting of the Texas Radiological Society was held at Abilene, Texas, on Jan. 16, 1937.

The following papers were presented:

Professional and Economic Problems of the Radiologist. CHARLES L. MARTIN, M.D., Dallas.

Discussion opened by W. S. HAMILTON, M.D., San Antonio.

The Need for a Broader Clinical Outlook by the Radiologists. J. W. CATHCART, M.D., C. H. MASON, M.D., and L. O. DUTTON, M.D., El Paso.

Discussion opened by DALTON RICHARDSON, M.D., Austin.

Hypertrophic Arthritis. PALMER E. WIGBY, M.D., Dallas.

Discussion opened by M. H. GLOVER, M.D., Wichita Falls.

Breast Radiography. G. D. CARLSON, M.D., Dallas.

Discussion opened by DAVIS SPANGLER, M.D., Dallas.

Diagnostic Bone Tumor Clinic. LEON J. MENVILLE, M.D., New Orleans, La.

Discussion opened by R. T. WILSON, M.D., Austin.

The Saturation Method of X-ray Treatment. TOM B. BOND, M.D., Fort Worth.

Discussion opened by R. H. MILLWEE, M.D., Dallas.

Symposium: X-ray Therapy in Inflammatory Conditions

X-ray Treatment in Acute Infections. JAMES D. WILSON, M.D., Lubbock.

Discussion opened by ROY G. GILES, M.D., Temple.

X-ray Treatment in Gas Bacillus Infection. J. J. FAUST, M.D., Tyler.

Discussion opened by W. G. MCDEED, M.D., Houston.

X-ray Treatment in Bronchopneumonia. JEROME H. SMITH, M.D., and F. T. MCINTIRE, M.D., San Angelo.

Discussion opened by ERLE D. SELLER, M.D., Abilene.

X-ray Treatment in Lobar Pneumonia. E. V. POWELL, M.D., Temple.

Discussion opened by L. R. TALLEY, M.D., Temple.

X-ray Treatment in Mastoiditis. C. F. CRAIN, M.D., Corpus Christi.

Discussion opened by J. M. SLOAN, M.D., Corpus Christi.

ANNOUNCEMENTS

FIRST INTERNATIONAL CONFERENCE ON FEVER THERAPY

The First International Conference on Fever Therapy will hold its sessions on March 29 30, and 31, 1937, at the College of Physicians and Surgeons, Columbia University, New York City. Please note that the dates have been changed from those previously sent for publication and to be found in RADIOLOGY, September, 1936, p. 375.

THE AMERICAN PUBLIC HEALTH ASSOCIATION'S SIXTY-SIXTH ANNUAL MEETING

The American Public Health Association announces that its Sixty-sixth Annual Meeting will be held in New York City, Oct. 5–8, 1937.

A large Eastern membership will receive that information with satisfaction. Not since 1921 has the Association met in the world's greatest city.

The Sixth-fifty Annual Meeting took place in New Orleans in October. It attracted an attendance of 1,650 health authorities representing 45 States, Canada, Cuba, Mexico and nine other foreign countries. The officers of the Association are reminding themselves of this registration in a State where the membership numbers less than 100 and asking themselves what the registration will be in New York City where the membership counts up to nearly 500 within the city limits alone. An overnight's ride will enable more than one-half of the Association's 5,000 members to attend the convention.

The National Organization for Public Health Nursing will meet with the American Public Health Association in 1937 for the first time. This large and important organization is expected to add another thousand to the registration lists.

The following related societies will meet with the Association as usual:

The American Association of School Physicians

International Society of Medical Health Officers

Conference of State Sanitary Engineers

Conference of State Laboratory Directors

Association of Women in Public Health

Delta Omega.

Dr. Reginald M. Atwater is the Executive Secretary of the Association, and the headquarters offices are at 50 West 50th Street, New York City.

BOOK REVIEW

"MEDICO-LEGAL ASPECTS OF FRACTURES." By EDWARD ADAMS, M.D., Lt. Col. U. S. Army, M.R.C. A volume of 168 pages, 62 drawings, and one anatomical chart. Bound in maroon buckram. Published by "The New York Physician," New York City, 1936. Price, $2.00.

This book, written by a distinguished New York surgeon, is an endeavor to be of service to the medical expert witness and to the lawyer who has to try bone injury cases, and in that respect the book is a decided success. It is sure to become invaluable to those who are trying to estimate the degree of disability and to determine the percentage of permanent incapacity which is liable to remain as the end-result in fracture cases.

As radiologists, we are frequently called upon to estimate the amount of permanent disability which is liable to occur in the end-result in fractures. These requests are becoming more frequent in the instances in which we appear before Industrial Commissions, and with the information to be gathered from this book we will be much better prepared to make these estimates in a manner to the satisfaction of all concerned.

The discussion of the various fractures, their causes, complications, and manner of repair is lucid and illuminating and definitely lays the foundation for a better appreciation of the importance of a knowledge of traumatic bone injuries.

Dr. Fred H. Albee, the well-known bone surgeon, wrote a Foreword in this book and says in part: "Many points in this book are so well taken as to invite comment. Everyone with any experience in compensation cases knows how widely physicians testifying in the same case may differ in their estimate of the disability. These physicians may be honest and more or less competent in their opinions, but they are not using the same measuring stick. They are looking at things from different points of view. The establishment of 'common ground' by offering practical standards such as the author presents for measuring disability is, therefore, most timely, and should do much to eliminate these annoying discrepancies of opinion which make matters exceedingly difficult for the court."

A glossary of medical terms of 19 pages is included, evidently for the benefit of attorneys, and to obviate the need for frequent reference to the medical dictionary.

The importance of the roentgenographic examination is stressed and thoroughly discussed. An entire chapter is devoted to this subject and more than a hundred legal decisions and references are cited.

This book is almost a *sine qua non* for those who treat a considerable number of fractures, particularly in industrial practice, as well as for those who are called in consultation in such cases. It should be extremely useful to those helping to adjudicate and evaluate personal injury, as well as to lawyers and the referees and examiners of Industrial Commissions.

The format, paper, and type are good. Except for a few errors in indexing which are of minor importance, the composition is good.

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Hans A. Jarre, M.D., of Detroit, Mich.
E. T. Leddy, M.D., of Rochester, Minn.
Ernst A. Pohle, M.D., Ph.D., of Madison, Wisc.
William R. Stecher, M.D., of Easton, Penna.
W. A. Sodeman, M.D., of New Orleans, La.
Charles G. Sutherland, M.B. (Tor.), of Rochester, Minn.

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GRENZ RAYS

The Technic of Grenz-ray Therapy in Nevus Flammeus. F. Kalz. Strahlentherapie, 1936, **57,** 510.

During the last few years the author has seen 49 cases of nevus flammeus: 31 of those were fully treated and observed, three are still under treatment, and the others could not be traced. Technic: Single doses of from 800 to 1,100 r, 12.5 kv., 7 cm. F.S.D., 15 ma., H.V.L. in Al, 0.026 mm., 1,990 r/min., total doses of 10,000–12,000 r. The results were so encouraging that the author recommends Grenz-ray therapy in nevus flammeus as the best therapy available to-day.

ERNST A. POHLE, M.D., Ph.D.

GYNECOLOGY AND OBSTETRICS

Relaxation of the Symphysis Pubis in Pregnancy. Herbert Thoms. Jour. Am. Med. Assn., April 18, 1936, **106,** 1364–1366.

Studies of various observers have revealed that relaxation of the symphysis begins in the first half of pregnancy, progresses but slightly in the last three months, and that retrogression begins immediately following delivery and is usually completed by the end of from three to five months. There is no essential difference between the behavior of the pelvic articulations in primiparas and in multiparas.

The author studied roentgenographically 100 primiparous women at different stages of pregnancy, and presents his findings in a table showing the variations in width observed. In the first half of pregnancy the minimum spread was 0.2 cm. and the maximum 0.6 cm.; in the second half the minimum was 0.3 cm. and the maximum 1 centimeter. No relationship between the amount of symphyseal relaxation and the pelvic type was apparent.

There is no doubt but that pelvic instability, incident to pregnancy changes in the pelvic joints and associated with symptoms of discomfort, is far more common than is usually supposed. These symptoms may include pain in the symphyseal region, backache and localized pain in one or both sacro-iliac joints, and difficulty in normal locomotion. One case is reported in which such pelvic instability assumed major proportions.

CHARLES G. SUTHERLAND, M.B. (Tor.).

The Indications for Radiation Therapy and Operation in Uterine Fibroid. C. Béclère. Strahlentherapie, 1936, **56,** 548.

The author outlines briefly the indications and contra-indications for radiation therapy of uterine fibroid. Provided the diagnosis is correct, roentgen therapy gives good results regardless of shape and size of fibroid and age of the patient. Determinations of the size of the tumor every eight days after treatment has been started is a valuable diagnostic aid. If menopausal symptoms appear, particularly hot flashes, and the bleeding continues, careful search for possible carcinoma of the fundus should be instituted.

ERNST A. POHLE, M.D., Ph.D.

The Utero-salpingogram as a Means of Differential Diagnosis in Gynecological Pathology. George Lyford. Jour. Med., November, 1936, **17,** 436–442.

Lyford points out that the immediate objection raised to the use of the utero-salpingogram is its danger in producing more or less serious complications to the pelvic pathology existing. However, in 1,752 examinations he has encountered only two complications, one an intra-abdominal pregnancy and the other a twisted pedicle cyst. Either of these conditions may have resulted from the examination or may have been purely coincidental. However, the percentage of complications is low and does not compare with the information it is possible to obtain. Results are dependent upon the ability of the observer to interpret both the fluoroscopic findings and the films. The fluoroscopic examination is an extremely important portion of the procedure. One must consider the utero-salpingogram as a laboratory procedure not to be used except as giving additional information when correlated with the other laboratory and clinical data.

W. A. SODEMAN, M.D.

HAY FEVER

Roentgen Therapy of Hay Fever. Laquerrière. Strahlentherapie, 1936, **57,** 70.

The author has seen some encouraging results in the treatment of hay fever by roentgen rays. The following technic proved satisfactory: 150 kv., 3 mm. Al, 30 cm. F.S.D., 150 r on the first and second days, to be repeated if necessary after five days, and 200 r after another five days if the condition of the patient requires it. Total doses of 1,000 r have not been exceeded. The eyes are covered with lead and the entire nose is in the field of exposure.

ERNST A. POHLE, M.D., Ph.D.

HEART AND VASCULAR SYSTEM

Right-sided Aortic Arch (Situs Inversus Arcus Aortæ). D. Evan Bedford and John Parkinson. British Jour. Radiol., December 1936, **9,** 776–798.

Right-sided aortic arch results from persistence of the fourth right embryonic arterial arch and the partial suppression of the fourth left embryonic arterial arch. This condition represents a reversion to the avian type of aorta, and thus to the pattern normally found lower in the vertebrate scale.

Other congenital cardiac malformations, such as Fallot's tetralogy, may be associated with right-sided aortic arch. In uncomplicated cases the aorta arises normally from the left ventricle, but if combined with Fallot's tetralogy, it arises from both ventricles and lies

somewhat to the right of its usual position. A right-sided aortic arch crosses the root of the right lung, instead of the left, and passes on the right side of the trachea and esophagus. It may descend the right side and cross the spine lower down. On the other hand, it may turn to the left behind the trachea and esophagus, after arching over the right bronchus. At this point an ampullary dilatation or a diverticulum is formed which pushes the trachea and esophagus forward and to the left. The left subclavian artery and sometimes the ductus arteriosus arises from this diverticulum. Below the level of the diverticulum the aorta may cross gradually to the left or it may pass to the right and then return to the left to reach the aortic opening in the diaphragm.

Two anatomical types of right-sided aorta have been recognized by Krause. In both types the aortic arch develops from the fourth right arterial arch. However, in the first type the proximal part of the left fourth arch persists as part of the left subclavian artery, while in the second type the distal portion of this arch forms an aortic diverticulum at the termination of the aortic arch, from which the left subclavian artery arises.

The radiological examination of right-sided aortic arch in the anterior position shows absence of the left aortic knob with the presence of a right aortic knob or a band-like shadow in this region. The visualized esophagus will be observed to be indented and to the left side of the arch. In the right oblique position, at the level of the arch, the visualized esophagus curves sharply forward and lies in front of the arch and diverticulum. When no diverticulum is present the aorta may not pass behind the esophagus, which, therefore, is not displaced. In the left oblique position it is observed that the aortic shadow in front of the trachea is wider than normal. The esophageal and tracheal displacement is less evident. The authors report eleven cases of right-sided arch and discuss the radiological features.

J. N. Ané, M.D.

The Simplest Aortic Measurement and its Physiologico-clinical Significance. Siegmund Kreuzfuchs. München. med. Wchnschr., April 24, 1936, pp. 681-683.

The author describes his most recent method of estimating the diameter of the aorta, and compares it to his earlier and well-known method. Inasmuch as the trachea and esophagus on their left aspect lie in the same sagittal plane as the bending margin of the contiguous aorta, one can measure orthodiagraphically the horizontal distance from the most prominent point along the left side of the aortic arch or knob, to the left tracheal margin. This affords an exceedingly simple and reliable estimate of the aortic diameter at this level, which approximates the site of the branching off of the common carotid artery. This measurement is slightly larger than the designated aortic-esophageal diameter as obtained by the original Kreuzfuchs method, due to the disparity in aortic diameters at the respective levels of the juncture of the common carotid and subclavian arteries, which produce fusiform regional aortic widenings. At a focal-film distance of 60 cm. the measurement obtained by the new method is magnified and distorted, and the corrected measurement can be readily deduced by subtracting one-sixth of this distance. A focal-film distance of 150 cm. requires a subtraction of one-fifteenth of the measured width. The average diameter of the aorta at this site is from 30 to 32 mm. in males and from 28 to 30 mm. in females. Contrary to former opinions, the aorta is not narrowed as age increases, for estimates obtained reveal that at 20 years of age, the aortic width is two-thirds the transverse vertebral body segment at the level of the fifth thoracic vertebra, whereas at 70 years it is equal to the vertebral body width.

The great importance from a physiologico-clinical concept, is the fact that the aorta under normal conditions presents extremely slight variance; the measurements for similar age, sex, and height being very constant; therefore, any aberrations are to be looked upon with grave suspicion as indicative of disease.

William R. Stecher, M.D.

A Multiloculated Non-syphilitic Aneurysm of the Aorta. S. Baumeyer. Deutsche med. Wchnschr., 1936, **62,** 1369.

The author describes an aneurysm of the aorta which was found during roentgen serial fluoroscopic examinations in a girl 21 years of age. The clinical examination as well as the Wassermann reaction was negative for syphilis. The roentgenogram showed a thin radiopaque line in the upper border of the aneurysm corresponding undoubtedly to calcium deposit. The author believes that the etiology is to be found in a congenital defect of the blood vessel wall.

Ernst A. Pohle, M.D., Ph.D.

A Radiologic Study of the Heart in Abdominal Typhoid. Giuseppe Pellegrini and Franco Facci-Tosatti. Archivio di Radiologia, 1936, **12,** 49–64.

In this study of 20 cases of typhoid, the authors used the method of Facci to measure the size of the heart and found that the size of the heart decreases 5 to 10 per cent during the course of the disease, due to a pathologic state of the circulatory system which reduces the venous blood inflow to the heart.

E. T. Leddy, M.D.

Roentgen Therapy of Angina Pectoris. R. Gilbert. Strahlentherapie, 1936, **57,** 203.

The author states that radiation therapy in angina pectoris offers definite clinical improvement in at least 50 per cent of all cases. High doses are to be avoided. He uses two large areas over the chest and one posterior area about 400 sq. cm. (180 kv., 0.7–1 mm. Cu + 1 mm. Al, 50 cm. F.S.D.). He starts in with a surface dose of 30 r in order to test the reaction of the patient and then increases this dose to 50 or 75 r. Three sittings

are given weekly. The entire course of treatments consists of 15 single sittings over a five-year period. Patients with fever, cachexia, and those over 70 years of age are not suitable for this type of treatment.

ERNST A. POHLE, M.D., Ph.D.

Atypical Roentgen Appearance of Pulmonary Infarction in Patients with Heart Failure. Hyman Levy. Am. Jour. Roentgenol. and Rad. Ther., May, 1936, **35,** 635–639.

In heart failure with pulmonary congestion, many more infarctions occur than are realized because of either the failure to recognize them clinically or their atypical roentgen appearance. The atypical situation and roentgen appearance are especially prone to be the case in pulmonary congestion, whereas the typical triangular density with the apex pointing to the hilum follows post-operative emboli.

The infarct density may persist for months or years. Two atypical cases are presented and the literature reviewed.

S. M. ATKINS, M.D.

Calcification of the Aortic Valve. L. Minor Blackford, William W. Bryan, and Emory D. Hollar. Jour. Am. Med. Assn., July 4, 1936, **107,** 18–21.

Calcification of the aortic valve was reported by Cowper in 1706, the gross appearance being beautifully illustrated at that time. Excellent descriptions were also recorded by Vieussens, in 1715, and Morgagni, in 1769. Osler described the condition in 1893. Interest in the subject was revived by a report of 42 cases observed at necropsy by Margolis, Ziellessen, and Barnes in 1931. The clinical aspects were discussed by Christian, in 1930 and 1931, who announced that Sosman had perfected a technic for demonstrating the calcification by fluoroscopic observation. The roentgenologic technic has since been described in detail by Sosman and Wosika (1933). To date, some fifty cases have been reported in the literature. The authors add one case in which calcification of all cusps of the aortic valve had been observed in fluoroscopic study and the findings were verified by roentgenograms of the heart after necropsy.

CHARLES G. SUTHERLAND, M.B. (Tor.).

Epipericardial Fat: Its Non-recognition a Common Cause of Error in X-ray Measurement of Heart Size. Sylvester McGinn and Paul D. White. Jour. Am. Med. Assn., July 18, 1936, **107,** 200, 201.

Much reliance is placed on x-ray measurement of heart size, provided certain sources of error are recognized and taken into account. The commonest cause of error has been that of distortion of the heart shadow by magnification when the x-ray tube is too close to the heart. This has been largely corrected by the use of the 6 to 7 foot (2 meters) distance from the film to the target.

The shape and position of the heart should always be considered, when making measurements. The presence of a triangle of epipericardial fat at the cardiac apex may cause an error in measurement. If this is included in the transverse measurement, it may cause an abnormal increase in the so-called cardiothoracic ratio, *i.e.*, the transverse measurement of the "heart" shadow may exceed half the internal diameter of the chest.

When the pericardial diaphragmatic angle is not clearly outlined and especially if it is obtuse, one may be suspicious of the presence of epipericardial fat. Fluoroscopic examination will often show two distinct shadows.

CHARLES G. SUTHERLAND, M.B. (Tor.).

THE HIP JOINT

Transitory Synovitis of the Hip Joint in Childhood. Jerome G. Finder. Jour. Am. Med. Assn., July 4, 1936, **107,** 3–5.

Transitory synovitis of the hip joint in childhood often remains unrecognized despite its relatively frequent occurrence. Usually the disease is erroneously diagnosed as tuberculosis of the hip. Other terms employed to designate this disease are: coxitis serosa seu simplex, coxitis fugitive, coxitis ephemere, coxitis fugax, coxitis incertae causae, and transitory arthritis of the hip joint. An underlying, non-specific infective focus is usually responsible. Trauma resulting from a fall, muscular strain (tap dancing and track athletics), contagion (measles and scarlet fever) have been considered factors. A definite syndrome of prodromal events for varying periods of time, followed by acute or insidious onset of limp, pain, night cries and restlessness, with tenderness to pressure, limitation of hip motion, and positive Patrick and Trendelenburg signs, characterizes the disorder. Roentgenograms are negative in their findings. Treatment is essentially conservative.

CHARLES G. SUTHERLAND, M.B. (Tor.).

INFLAMMATORY DISEASES

Roentgen Therapy of Inflammatory Disease. G. Charmandarian. Strahlentherapie, 1936, **57,** 187.

The author recommends the use of roentgen rays in the treatment of inflammatory disease. His results are essentially the same as those reported in the literature. Doses of from 10 to 30 per cent E.D. (150 kv., 5 mm. Al or 0.5 mm. Cu + 1 mm. Al) are usually applied.

ERNST A. POHLE, M.D., Ph.D.

THE KIDNEYS

Pyelography of the Surgically Exposed Kidney. Herman L. Kretschmer and Faye H. Squires. Jour. Am. Med. Assn., July 18, 1936, **107,** 205.

In the case reported a pre-operative diagnosis of

right renal tuberculosis was made without the benefit of ureteral catheterization or intravenous urography. At operation the kidney appeared normal. Ten centimeters of diodrast was injected into the unopened pelvis and a roentgenogram was made. This showed findings indicative of renal tuberculosis and all doubt about the propriety of nephrectomy was removed.

CHARLES G. SUTHERLAND, M.B. (Tor.).

THE KNEE JOINT

Roentgen Therapy of Extensive Periarthritis of the Knee Joint. G. Huc and P. Aime. Strahlentherapie, 1936, **57,** 270.

The authors recommend the use of roentgen therapy in periarthritis of the knee joint. They have used it in over 300 cases and developed the following technic: They begin with 75–125 r (0.5 mm. Cu + 1 mm. Al, 30–40 cm. F.S.D.) and increase this slowly to 200–250 r per field. One area is given per sitting with a total of two lateral, one anterior, and one posterior field. The total dose amounts to from 1,500 to 2,700 r over four areas, *i.e.*, 375 to 675 r per field. The entire treatment takes three or four weeks; at least seven, but not more than twelve, sittings should be given. A slight reaction sometimes occurs after the first exposure. As a rule, one series of treatments sufficed; in 6 per cent only of the cases was the second necessary. Improvement should be noticeable after the fourth treatment. Appended roentgenograms show that, although the radiological findings were unchanged after the treatment, the clinical improvement was most satisfactory.

ERNST A. POHLE, M.D., Ph.D.

THE LUNGS

Diagnosis and Treatment of Pleural Empyema. Richard Goldhahn. München. med. Wchnschr., April 24, 1936, pp. 676–678.

A brief review of clinical signs and symptoms is given, the author cautioning against heavy percussion, which might produce no elicited dullness due to "empyema being percussed through." Diagnosis is imperative and fairly good sized encapsulated empyemas can be overlooked. Roentgenograms are, therefore, essential, particularly in localization of encapsulated interlobar collections of fluid. Another useful function of x-ray examination is the determination of whether or not pneumothorax is present.

Paracentesis thoracis is useful only for diagnostic purposes and drainage should not be attempted from this alone. Especial caution should be taken to prevent entrance of air into the pleural space. The *rationale* of a closed drainage is well outlined, by showing how a so-termed "low encapsulated empyema" is produced in contradistinction to a high empyema when a pneumothorax is produced—for the air goes to the apex of the pleural cavity, preventing expansion of the lung apex, and thereby producing an elongated path from this cephalad portion of the empyema to the drainage site. This entity the author calls a "high situated empyema." Inasmuch as paracentesis alone is rarely effectual, the author recommends early thoracotomy of the closed type, which permits the lung apex to expand first. Other advantages of the latter are the prevention of venous stasis and cyanosis, as occasionally occurs when a pneumothorax is present, preventing re-expansion of the lung.

WILLIAM R. STECHER, M.D.

Congenital Cystic Disease of the Lungs: A Clinico-pathological Study. Samuel George Schenck. Am. Jour. Roentgenol. and Rad. Ther., May, 1936, **35,** 604–629.

This disease is now an established clinical entity readily recognized during life. In infants and young children, the prognosis is grave; in older patients, thoracic surgery such as lobectomy offers hope.

The symptomatology depends on the size of the cyst or cysts, their location and whether or not they are infected. Cough, dyspnea, cyanosis, and expectoration are commonly found; fever, malnutrition, thoracic pain, hemoptysis, weakness, wheezing, anorexia, palpitation, and vomiting may also occur. When infection occurs suppurative symptoms naturally supervene. Some patients may have no symptoms at all.

Roentgenologically, if the cyst be solitary and fluid-containing, it is an ovoid opaque area in the parenchyma of the lung and remains unchanged over a long period of time. Following rupture, a horizontal fluid level is seen with air above. With the fluid completely replaced by air, the wall is seen and appears thin. Fine strands in wide sweeping curves are frequently seen traversing the cyst.

The multiple cysts, which are usually smaller than the solitary, may be scattered in more than one lobe and, except for the history dating back to infancy, are more difficult to differentiate from acquired bronchiectasis. An artificial pneumothorax will differentiate a large cyst from pneumothorax by demonstrating the cyst within the lung.

The literature of this condition is reviewed, 232 cases analyzed, and 4 new cases presented and described in detail, covering the history, incidence, etiology, pathology, classification, clinical types, symptoms, clinical course, roentgenologic findings, differential diagnosis, complications, prognosis, and treatment.

S. M. ATKINS, M.D.

Primary Malignant Disease of the Tracheobronchial Tree: Report of 140 Cases. Porter P. Vinson. Jour. Am. Med. Assn., July 25, 1936, **107,** 258–260.

Metastatic nodules in the lungs, even though they may be large and numerous, rarely produce signs or symptoms of pulmonary disease unless they involve the pleural surfaces and cause pain or effusion into the pleural space. They may be unsuspected until a roentgenogram of the thorax reveals their presence. A small growth arising in a bronchus may soon reduce the

lumen of the tube and interfere with drainage to such an extent that suppurative processes may mask the underlying disease. The chief factor in the more frequent antemortem recognition of primary malignant growths in the air passages has been the more general employment of bronchoscopy in the diagnosis and treatment of chronic pulmonary diseases and the removal of tissue for microscopic examination.

Roentgenographic examination revealed the presence of a lesion in 136 of the 140 cases reviewed in this series. In one case not recognized roentgenographically the tumor was situated in the trachea; in three others the lesion was situated in the lumen of a bronchus and examination failed to reveal the presence of the disease.

CHARLES G. SUTHERLAND, M.B. (Tor.).

Congenital Cysts of the Lung from the Roentgenologic Viewpoint. B. R. Kirklin. Am. Jour. Roentgenol. and Rad. Ther., July, 1936, **36,** 19–29.

Anatomically the cavities are either bronchial dilatations or cavities resembling blebs lying subpleurally. Between these extremes are all sorts of gradations and transition types. They may or may not communicate with the bronchi, be single or multiple, contain air or fluid, or both.

Clinically, dyspnea, cyanosis, cough, cardiac palpitation, and (rarely) hemoptysis may occur; much depends on their size and location, and in the small cysts practically no symptoms may be present.

Roentgenologically the signs vary according to their content, size, number, location, and the presence or absence of complications. In most cases the more common diseases which they resemble, such as bronchiectasis, abscess, tuberculosis, dermoid or hydatid cyst, must be diagnosed, but this condition considered. The small multiple cysts and the larger single cyst should be more easily diagnosed correctly in view of the fine apparent non-inflammatory walls.

S. M. ATKINS, M.D.

LYMPHOGRANULOMA

Our Experience in the Treatment of Lymphogranulomatosis. W. Baensch. Strahlentherapie, 1936, **56,** 541.

The author outlines briefly his experience in the treatment of Hodgkin's disease, based on 23 cases seen during the period from 1925 to 1930, and 55 cases observed during the period from 1931 to 1936. He deduces from these figures that there is an increase in the occurrence of the disease, although this might be explained partly by an improvement in our diagnostic facilities. As to the etiology, the author feels that Hodgkin's disease is probably a special type of tuberculosis. Radiation therapy should be applied as little as possible and only when necessary to keep the patient comfortable; the average dose per field is 150 r. Radium is as effective as roentgen rays but seems suitable only for superficial glands. The average duration of life in the author's cases was two years. However, some responded better to the treatment: one lived 11, three lived 6, three lived 4, and three lived 3 years after the diagnosis had been made.

ERNST A. POHLE, M.D., Ph.D.

MASTITIS

The Value of Roentgen Therapy in the Treatment of Puerperal Mastitis. C. Margraf. Strahlentherapie, 1936, **57,** 303.

The author relates his experience with the treatment of puerperal mastitis by roentgen rays. Technic: 115 r per sitting, 172 kv., 0.5 mm. Cu + 1 mm. Al, 30 cm. F.S.D., 48.6 r per minute. This dose is repeated after 48 hours, provided the first exposure did not bring complete relief.

The author's material consisted of 245 cases; 127 were treated conservatively and 118 patients were treated by roentgen rays. Subtracting those cases that were too far advanced for irradiation, the percentage of cure without surgical intervention amounted to 81 per cent. It is important to treat the patients early; that is, within 24 hours after the first symptoms.

ERNST A. POHLE, M.D., Ph.D.

MEDIASTINAL DISEASES

Radiation Therapy of Mediastinal Diseases in Children. R. Sarasin. Strahlentherapie, 1936, **57,** 140.

The author gives an outline of the dosage and technic used in the treatment of mediastinal diseases in children. In hyperplasia of the thymus, 30 r every two to five days are given. The dose may be increased to from 50 to 80 r. Deep therapy technic is used; the total dose does not exceed 300 to 700 r. In malignant tumors of the thymus, 70 r are given daily over from two to four areas, depending on the age of the child. A total dose of 5,000 r usually suffices to bring about regression of the neoplasm. In lymphosarcoma, 50 r are given daily and may be increased later to 150 r. The blood picture has to be checked carefully. In Hodgkin's disease treatments are given once or twice daily, 100–180 r per sitting with total doses up to 3,500 r. In lymphatic leukemia, general body exposure seems to be the method of choice; from 8 to 15 r per sitting should not be exceeded. The enlarged glands sometimes require local exposure of from 50 to 100 r every three days. Enlarged tracheobronchial glands may respond to from 40 to 80 r per sitting, given twice weekly, up to 1,500 r over a six to eight weeks' period. Pott's disease is treated with a similar technic. In tuberculosis of the hilum glands as well as in mediastinal pleuritis, roentgen therapy is contra-indicated. There are a number of lesions which might be erroneously diagnosed mediastinal tumors as, for instance, congenital diseases of the heart, idiopathic dilatation of the esophagus, cysts and ectopic lobe of the thyroid gland. Radium may also be used but only in the form of telecurietherapy with one or more grams of radium.

ERNST A. POHLE, M.D., Ph.D.

MYOSITIS OSSIFICANS

Traumatic Myositis Ossificans: The Result of Injury or Treatment? Lorenz Böhler. München. med. Wchnschr., April 10, 1936, p. 594.

The author concludes that myositis ossificans, if making its appearance fairly early after an injury, is not the result of the trauma *per se*, but is mainly caused by the treatment. This, he states, is due to the commonly practised excessive early massage and passive motion of the affected part. He considers healing to be enhanced by therapeutic *noli me tangere*, and condemns medico- and physio-therapeusis.

WILLIAM R. STECHER, M.D.

OSTEOMYELITIS

Osteomyelitis of the Inferior Surface of the Petrous Pyramid. Wells P. Eagleton. Jour. Am. Med. Assn., Aug. 15, 1936, **107,** 482–484.

Apicitis is a generic term, covering a large number of different pathologic states, the symptoms of which are modified by the surrounding parts. Because of the peculiar nature of the bone, the pathologic process in the vast majority of cases has a tendency to (*a*) spontaneous cure, while about 15 per cent end in (*b*) abscess formation, many cases of which to-day are saved by well-directed treatment, while a very few, approximately 5 per cent, continue throughout as (*c*) invasive forms of thrombophlebitis and are uniformly fatal.

Each variety of petro-apicitis requires clinical differentiation because the specific line of treatment to be adopted depends not only on the nature of this lesion but on its anatomic position in the bone. The petrous apex, from a pathologic and surgical standpoint, is divisible into three domains: (1) The marrow-filled osseous matrix itself, with its dural coverings on its anterior and posterior surfaces. (2) The domain of the carotid canal, which, passing through the petrous apex, contains the carotid artery surrounded by its carotid venous plexus and (3) the inferior "cribriform" perforated plate on the pharyngeal surface of the apex.

The clinical and surgical aspects are discussed in detail.

CHARLES G. SUTHERLAND, M.B. (Tor.).

THE PANCREAS

The Problem of Cancer of the Pancreas. Howard M. Clute. Jour. Am. Med. Assn., July 11, 1936, **107,** 91–97.

Cancer of the pancreas is by no means a rare disease. It would be safe to assume that 3 per cent of all cancer deaths arise from cancer of the pancreas and total 4,000 a year in the United States.

The malignant process may originate in the parenchyma of the gland, in the pancreatic ducts or, rarely, in the islands of Langerhans. The most frequent type of tumor is the adenocarcinoma, although scirrhous forms are not infrequent. Most pancreatic tumors are primary in the pancreas, but a very few are primary in the biliary tract or duodenum and invade the pancreas secondarily. The tumor is most frequently located in the head of the gland.

In every patient thorough gastro-intestinal x-ray study should be done to rule out lesions in the stomach, duodenum, gall bladder, or colon. A wide sweep of the duodenum around the head of the pancreas may be noted, or the greater curvature of the stomach may be encroached on by an obviously extra-gastric lesion. Engel and Lysholm have attempted to obtain special films of the pancreatic area by first giving the patient an effervescing powder to fill the stomach with gas. They then take lateral and antero-posterior plates and believe they can outline pancreatic tumors in certain cases. Further progress in x-ray technic will aid in earlier diagnosis of these cases.

CHARLES G. SUTHERLAND, M.B. (Tor.).

PAROTITIS

Roentgen Therapy of Post-operative Parotitis. Heinz Knüpper and Rudolf Hummel. München. med. Wchnschr., April 24, 1936, pp. 679, 680.

The authors contribute an excellent and rather comprehensive study of a condition which is but meagerly referred to in the roentgen literature. A total of 59 cases was studied, with 21 of these utilized as controls and receiving no roentgen therapy. The authors conclude that the most favorable time for irradiation is immediately one arrives at a diagnosis, and at this stage the condition generally can be aborted. In the majority of the cases in the late stages of the disease, surgical incision was necessary in conjunction with irradiation. Thus, 24 of 26 cases which were irradiated from the first day of the onset of the condition, required no further treatment; in contrast were 10 of 17 cases in the later stages, which required incisions. In the non-radiated control group, 10 of 15 required surgical intervention and of these six died. In early cases the parotitis is aborted, and, if more advanced, there is more rapid softening. with ensuing suppuration with the aid of x-radiation. Pain is alleviated and fever is abated. An important consideration is the shortening of the period of hospitalization in those cases irradiated.

In the majority of cases a dose of from 150 to 200 r is administered, employing the following physical factors: 190 kv.; 3.5 ma.; 0.5 mm. Cu and 3.0 mm. Al filtration (S.T.D. not given). This may be repeated in two days if necessary and, in refractory cases, three doses may be indicated.

WILLIAM R. STECHER, M.D.

PEPTIC ULCER

Further Observations on Roentgen Therapy in Peptic Ulcer of the Stomach and Intestines Treated According to Our Method. M. Nemenow and A. Jugenburg. Strahlentherapie, 1936, **57,** 327.

During the period 1934–1936 the authors observed

336 patients with peptic ulcer. Forty-one were located in the small curvature; 41, in the pyloric region; 133 had duodenal ulcer; seven had ulcers in the duodenum and in the small curvature; 25 had periduodenitis; 25, jejunal ulcer following gastro-enterostomy; 16, gastrojejunitis; 18, strictures in the pylorus with peptic ulcer. Technic: one anterior and one posterior area of 10 × 15 sq. cm., 30 cm. F.S.D. Each field receives twice 225–250 r at four- to six-day intervals. Following this local irradiation, the celiac ganglion is irradiated. A field 8 × 15 cm. in the region of thoracic vertebræ 5 to 12 receives two exposures of 225–250 r each at 4- to 6-day intervals. Patients with chronic constipation are treated, in addition, over two areas in the lumbosacral area. The results were gratifying: 38.8 per cent were cured and 52.43 per cent improved; 8.68 per cent remained unchanged.

In conclusion, the authors state that roentgen therapy applied according to their method is the method of choice in treating peptic ulcer. It should be given a trial before operation.

ERNST A. POHLE, M.D., Ph.D.

RADIUM

Investigations Regarding the Problem of Radium Poisoning. I. Toxic Quantities of Radium Introduced into the Human Body. B. Rajewsky. Strahlentherapie, 1936, **56,** 703.

The author undertook a series of measurements in persons with radium poisoning and compares his results with those published in the literature. He establishes as toxic dose for the internal application of radium the quantity of one microgram radium element of "Restradium." The tolerance dose for internal radium administration is also discussed.

ERNST A. POHLE, M.D., Ph.D.

Measurement of the Doses in Radium Therapy. J. Murdoch, E. Stahel, and S. Simons. Strahlentherapie, 1936, **57,** 87.

The authors use the "roentgen" in expressing their doses in radium therapy. According to their measurements, 1 mg. of radium filtered through 1 mm. Pt emits 7.62 r per hour at 1 cm. distance. They publish a number of tables which permit the determination of the dose applied for various types of radium moulds at distances of 1, 2, 3, and 5 centimeters.

ERNST A. POHLE, M.D., Ph.D.

Effects of Radiation on the Cadaver (Radiothanatology). G. G. Palmieri and G. Paltrinieri. Strahlentherapie, 1936, **57,** 94.

The authors propose and have started an extensive program of research dealing with the effect of various types of radiation on the cadaver, and in this paper they briefly describe a few of their preliminary experiments and findings. Heavy irradiation by radium rays did not produce any microscopic changes in the skin of a dead human being, if given within three hours postmortem. This suggests the use of the procedure as a test for death.

ERNST A. POHLE, M.D., Ph.D.

A Combined Radium Localizer. R. Werner. Strahlentherapie, 1936, **57,** 385.

The author describes a radium bomb developed in his clinic. It is constructed in such a manner as to require only relatively small amounts of radium element (300 mg.). At 5 cm. the output is 78 r per hour, and with 500 mg., 126 r per hour. Assuming the intensity at 5 cm. distance would be 100 per cent, it amounts to 37 per cent at 10 cm. Photographs of the entire apparatus and isodose curves in r per minute for 300 mg element are shown with the article.

ERNST A. POHLE, M.D., Ph.D.

A Cyclic Occurrence of the Radium Erythema and a Paradox "Pale Reaction" Following Radium Exposure of the Comb and Wattles of the Rooster Due to Changes in the Collagen. E. Zurhelle. Strahlentherapie, 1936, **57,** 473.

The author studied the reactions of the skin in man and on the comb and wattles of roosters, both microscopically and macroscopically following exposure to gamma rays of radium. He found that the erythema reaction appeared in cycles, while the microscopical studies showed marked changes in the collagen of the connective tissue. Based on his observations, he proposes a classification of the reaction in five different stages. For details, see the original.

ERNST A. POHLE, M.D., Ph.D.

Late Results of Radium Therapy of Cavernous Hemangioma in the Face of Children. F. Perussia. Strahlentherapie, 1936, **57,** 109.

The author relates his experience in the treatment of hemangioma of the face with radium. Several case histories are briefly quoted and photographs of eight cases before and after treatment show the results obtained by this method.

ERNST A. POHLE, M.D., Ph.D.

Radium Therapy in Angioma Planus. A. Marin. Union Méd. du Canada, May, 1936, **65,** 446–449. (Reprinted by permission from British Med. Jour., Oct. 3, 1936, p. 55 of Epitome of Current Medical Literature.)

The author maintains that the treatment of angiomas differs according to their variety. The stellate forms respond well to the galvanic cautery, electrolysis, electro-desiccation, and carbonic snow. In the tuberous forms, which are globular, more or less prominent, and of variable size, radium, applied either externally or by puncture, gives excellent results—radium puncture is the preferable method. The radium-containing needle should be introduced into the middle of the

angiomatous mass, and left for some hours. The irradiations cause an obliterating arteritis, the dilated vessels become obliterated, and the angioma disappears. As the reaction occurs in the middle of the nevus the skin is unaffected, and a disfiguring radiodermatitis does not result, as in external applications of radium. Tuberous prominences are often present in angioma planus, and these respond well to radium puncture. This treatment is not completely successful in every case, but improvement always occurs. To be successful, the essential need of early treatment (during the first year of life) is emphasized. An illustrative case is recorded.

The Radium Safe of the Portuguese Institute for Oncology. F. Bénard-Guedes. Strahlentherapie, 1936, **57,** 181.

The author briefly describes a special safe constructed for the storing of radium. It offers ample protection to those handling the radium applications. Two sketches are appended.

ERNST A. POHLE, M.D., Ph.D.

ROENTGEN-RAY BURNS AND INJURIES

Experience as to the Tolerance for Roentgen Rays and its Application in the Prevention of Injuries. H. Holthusen. Strahlentherapie, 1936, **57,** 254.

The author studied the injuries to normal tissue appearing after exposure to large doses of roentgen rays and radium. Using the Coutard method, the percentage of telangiectasis increased from 10 per cent for total doses of from 2,500 to 3,000 r, up to 100 per cent for total doses of 5,000 r and more. In a table the number of cases of telangiectasis and induration of the skin for high doses of roentgen rays and radium in relation to the number of fields are compiled. To-day thorough tumor irradiation does not exclude late injuries with certainty, but further improvements in our technic will probably reduce the percentage.

ERNST A. POHLE, M.D., Ph.D.

Chronic Roentgen Injury of the Toes, Dorsum of the Foot, and Anterior Lower Thigh in a Radiologist. A. Köhler and W. Brock. Strahlentherapie, 1936, **57,** 49.

The authors, a radiologist and a dermatologist, describe chronic changes occurring in the toes, dorsum of the foot, and lower leg of the former. The changes in the thigh were those of atrophy, seen and described in other parts of the body, following exposure to small doses of roentgen rays over a long period. Most striking were the changes in the nails of the first and second toe: one seemed to be entirely destroyed but there was no inflammation. The nail itself was of a dark brown color and thickened to about 7 mm.; the nail bed was not exposed at any place. This type of change has not been described so far in the literature.

While writing the article, the authors received a communication from another radiologist, 50 years of age, who, after 25 years of practice in radiology, noticed reactions similar to those described in the article

ERNST A. POHLE, M.D., Ph.D.

The Danger of Radiation Injuries. R. du Mesnil de Rochemont. Strahlentherapie, 1936, **56,** 671.

After an analysis of our present knowledge regarding the tolerance of the skin to roentgen rays as applied to the various customary methods (single, massive, fractional, protracted fractional, saturation), the author reports five cases of late injuries. He concludes that in spite of our accurate physical measurements of the dose which render radiation therapy in skilled hands quite safe, there still remains the danger of injury because of our limited knowledge of the recovery periods of normal tissue.

ERNST A. POHLE, M.D., Ph.D.

Intra-uterine Fetal Injuries. H. Naujoks. München. med. Wchnschr., June 26, 1936, **83,** 1039–1044.

An exhaustive review of the etiology of fetal injuries is presented, and a rather brief allusion to the rôle of radiotherapy, both radium and x-rays, is made. The author makes a distinct division regarding the potential ultimate damage that might ensue to the fetus, when a non-pregnant woman is irradiated, the effects being cumulative in the ovaries, and the direct effect upon the growing fetus during gestation. The former question is still indecisively settled, there being opinions for and against its possibility and frequency. However, in regards to the latter, there is incontrovertible evidence showing the dire consequences that have followed injudicious radiotherapy.

The author has observed cases in which the fetus showed generalized deficient growth, mental retardation, and development of microcephaly and idiocy, as well as sundry other changes such as ocular disturbances, changes in the blood picture, etc. In one example, normal first and third children were delivered, but the second child was a dwarfed microcephalic, later showing paralytic changes and idiocy. This fetus had received irradiation inadvertantly during its early formation, *i.e.*, during the first three months of intra-uterine life. The author strongly urges the detection of early pregnancy in cases in need of deep radiotherapy, and the proper treatment of these patients, before irradiation is administered.

WILLIAM R. STECHER, M.D.

Radiation Injuries Following Treatment of Skin Tuberculosis. W. Schultze. Strahlentherapie, 1936, **57,** 165.

Roentgen rays must be used cautiously in the treatment of tuberculosis of the skin. The author saw 17 cases with roentgen injuries in a relatively short period. Even Grenz rays may be responsible for late reactions. A series of photographs is appended to the article demonstrating the lesions.

ERNST A. POHLE, M.D., Ph.D.

ROENTGEN SICKNESS

Liver Extract as a Remedy for Roentgen Sickness. Barton. R. Young. Am. Jour. Roentgenol. and Rad. Ther., May, 1936, **35,** 681–688.

Liver therapy should be used routinely for roentgen sickness. In 30 cases in which it was employed, complete relief of the nausea and vomiting occurred in 53 per cent, while 23 per cent showed definite decrease of symptoms, and 23 per cent were failures. No harmful effects have been noted. Roentgen intoxication is also benefited.

Two c.c. of liver extract are injected daily, either intramuscularly or intravenously, either just before or shortly after the treatment. The response may be prompt or gradual.

S. M. Atkins, M.D.

SILICOSIS

Diagnosis of Silicosis, with Special Reference to Roentgenological Manifestations. L. U. Gardner. Ann. Int. Med., August, 1936, **10,** 166–173. (Reprinted by permission from British Med. Jour., Nov. 28, 1936, p. 87 of Epitome of Current Medical Literature.)

The author thinks that even in the presence of a history of exposure to dust a diagnosis of silicosis should not be made until generalized discrete nodular shadows are seen on the radiograph of the lungs. Large localized shadows suggest complicating infection, but there is also a conglomerate type of silicosis that occurs in the absence of active infection. It may, of course, result from pulmonary damage by a previous infection that has healed. It can be differentiated from active infection only by careful clinical study and by repeated radiographic examinations to exclude change in the character and size of the lesions. The silicotic lung may exhibit the usual manifestations of tuberculosis, superimposed upon a background of generalized nodulation; more common are the massive foci of consolidation due to silico-tuberculosis. These may be situated in the upper parts of the lung, where they result from re-activated apical tuberculous foci, but often they occur in the middle and lower zones of the lung. They are the result of a combination of very chronic tuberculosis and silicosis progressing simultaneously in the same area. They give rise to much less pronounced symptoms of intoxication than tuberculosis alone. More acute forms of tuberculosis, aspiration disease, and miliary tuberculosis occur, but they are not common. Non-siliceous dusts are generally responsible for an accentuation of the linear markings of the lungs. As far as is known, the slight perilymphatic reactions responsible for them do not interfere with pulmonary function, and they do not alter the individual susceptibility to tuberculosis.

Asbestosis is not so well understood. The radiograph shows a diffuse haziness of the lower lung-fields, and later a very fine uniform stippling. Whether the chronic pleurisy, the increased linear markings, and the conglomerate shadows are due to dust or to the secondary changes incident to collapse of lobules or to complicating infection has not been definitely settled. The appearance of a tuberculous lesion in the asbestosis lung is apparently not modified. There may be some tendency toward chronicity.

THE SKIN

The Keloid and its Cure by Radiation Therapy. A. Hintze. Strahlentherapie, 1936, **57,** 224.

The author treated keloids with roentgen rays and radium and found that they were both effective. Severe reactions should be avoided. In comparing the end-results, he found that the normal consistency of the skin reappears with more certainty if radium is used. The skin in the treated areas is also more pliable. A number of illustrations of successfully treated cases are appended. His report is based on 26 patients observed in his clinic during the last 14 years.

Ernst A. Pohle, M.D., Ph.D.

Studies of the Permeability of Membranes of Human Skin and its Relation to the Effect of Roentgen Rays on Living Tissue. L. Neu and V. Neu. Strahlentherapie, 1936, **56,** 692.

The authors determined the electric conductivity of the skin of the forearm for a period of 12 days. Then they exposed the volar side of the right arm to roentgen rays (150 kv., 30 cm. F.S.D., no filter, 72 r per minute, doses varying from 4 to 8 minutes). They found that the permeability of the cell membrane may be increased after roentgen exposure and particularly in cases in which the membrane equilibrium is unstable before the irradiation. They conclude from these experiments that tissue with labile cell membranes has an increased radiosensitivity.

Ernst A. Pohle, M.D., Ph.D.

THE SPINE

The Differential Diagnosis between Infection and Malignancy in Cases of Dorsal Paravertebral Mass. Walter W. Fray. Am. Jour. Roentgenol. and Rad. Ther., May, 1936, **35,** 591–603.

Three cases of malignant tumors of the spine are described and their differentiating features from masses produced by tuberculous and non-tuberculous infections and benign growths.

The important features of malignancy are as follows: (1) preservation of the articular plates in the presence of collapse of the body; (2) slight or no narrowing of disc spaces in cases of marked collapse; (3) absence of wedging; (4) diffuse increase in bone density and involvement of the appendages of the vertebra.

S. M. Atkins, M.D.

THE STOMACH

Lymphoblastoma of the Stomach: Report of Case, with Especial Reference to the Gastroscopic Appear-

ance. John F. Renshaw. Jour. Am. Med. Assn., Aug. 8, 1936, **107,** 426–428.

This is a report of a case, with especial reference to the gastroscopic appearance. The roentgenologic examination of the stomach revealed markedly enlarged rugæ which could not be obliterated by pressure. This was interpreted as due to a marked submucosal infiltration which had not broken through the mucosa; from the x-ray examination alone it was not possible to differentiate definitely between a marked hypertrophic gastritis, a submucosal infiltrating carcinoma and, in view of the biopsy, an infiltrating lymphoblastoma.

The gastroscopic findings were similar to those reported in the other two cases observed gastroscopically and reported. In these two there was a diffuse infiltrating process involving the whole stomach. In the author's case the process was circumscript. Without knowledge of the cervical biopsy and the response to radiation therapy, the diagnosis of lymphoblastoma of the stomach would not have been made.

Schindler believes that the appearance of the diffuse infiltrating process is characteristic and cannot be mistaken for anything else. In contrast to the diffuse type, the circumscript lymphoblastoma is less characteristic.

CHARLES G. SUTHERLAND, M.B. (Tor.).

The Roentgenologic Appearance of the Resected Stomach. Giovanni Baldelli. Arch. di Radiologia, 1936, **12,** 9–41.

In this study Baldelli illustrates and discusses the physiology and mechanics of the stomach after resection. Because of the detailed extent of his findings it is suggested that the paper be consulted in the original.

E. T. LEDDY, M.D.

SYPHILIS

Contribution to the Etiology of Cancer. R. Gassul. Strahlentherapie, 1936, **57,** 20.

After a general discussion of the various theories regarding the etiology of cancer, the author relates the history of a male patient, 33 years of age, who entered the clinic with an ulcer of the penis and glandular swelling in the right groin. At the age of 19 he had had typhoid fever; at 24 years, syphilis, and at 29, malaria. Microscopic examination after admission to the clinic showed the presence of *Streptobacillus Ducrey-Unna*. The Wassermann reaction was negative. Local treatment brought about healing of the ulcers. In the glands of the right groin, fluctuation developed; treatment was by incision and drainage. The wound showed very little tendency to heal and within a few months developed into a large ulcer 11 × 4 cm. and 4 cm. deep. A biopsy, taken from the margins, showed carcinoma. A course of x-ray therapy was given, but not completed because the patient left the hospital. He was brought in three months later because of hemorrhage from the ulcer and it appeared that the carcinoma had eroded the large vessels of the thigh. The patient died within a few hours after admission.

From this observation the author concludes that it is advisable to take biopsies in cases of inflammatory disease accompanied by ulceration and proliferation of tissue. Particularly in the case of a chancre, the possibility of a developing malignancy should be considered.

ERNST A. POHLE, M.D., Ph.D.

THE TEETH

Changes in Teeth Following Protracted Fractional Roentgen Therapy. M. Lüdin and O. Müller. Strahlentherapie, 1936, **56,** 644.

Roentgen injuries of the adult tooth have been reported so far in only two instances; the authors add to these one case of their own. It occurred in a male, 45 years old, who received 40 sittings over three fields during four weeks according to the Coutard method and a total of 6,990 r. Three months after the treatment the crowns of the teeth located within the treated area became soft, showed brown discoloration, and developed defects in the enamel. Histologic examination of the extracted teeth showed definite changes in the pulp and periodontium. Since no other explanation for these peculiar changes could be found, the authors assume that they were due to the exposure to roentgen rays. They conclude that in cases of this type the teeth should be shielded by adequate protective materials.

ERNST A. POHLE, M.D., Ph.D.

THE THYMUS

The Radiotherapy of Thymic Hypertrophy. Enrico Benassi. Archivio di Radiologia, 1936, **12,** 65–69.

The author reports "brilliant results" by the use of a cycle of five treatments given every two days with from 80 to 120 r through an anterior thoracic field 6 × 8 cm. with 150 kv., 2–4 ma., 30 cm. T.S.D., and filtration of 0.3 mm. zinc + 3 mm. Al. This is repeated in from six to eight weeks. This technic may be modified as occasion requires. (The author does not state the number of cases he has treated.)

E. T. LEDDY, M.D.

Primary Carcinoma of the Thymus Gland: Case Report. H. A. Slesinger. Jour. Lab. and Clin. Med., November, 1936, **22,** 151–155.

The rarity of carcinoma of the thymus gland is indicated by the fact that, including the author's patient, only 53 cases have been reported. The clinical picture of all thymic tumors is the same. There is nothing to distinguish a carcinoma from a lymphosarcoma clinically except the response of the latter to radiotherapy. Symptoms are those of pressure in the upper portion of the mediastinum. Exophthalmos is frequently encountered. X-ray examination shows a tumor which is located in the upper portion of the anterior mediastinum. Symptoms usually appear late, often not until a few weeks or months before death. Treatment is unsatisfactory. Carcinoma of the thymus gland is not radiosensitive.

W. A. SODEMAN, M.D.

TUBERCULOSIS

Pathogenesis of Tuberculosis. Max Pinner. Jour. Am. Med. Assn., Aug. 15, 1936, **107,** 475–477.

The first infection is, in the vast majority, by inhalation and the first focalization is in the pulmonary parenchyma. As far as the bacillus is concerned, the pathologically most important characteristics are its high resistance, its singularly complete adaptation to parasitic life, its relative virulence, the dosage of infection, and its chemical constituents which stimulate or alter more or less specifically different tissue elements. The first infection causes two potentially permanent alterations in the host: it produces allergy and it establishes within the body a deposit of tubercle bacilli.

The reality of endogenous reinfection is proved beyond doubt by the frequent occurrence of foci in localizations that could not possibly be reached by direct exogenous reinfection, such as the skeletal system, the urogenital tract, or the brain. The immunologic change that is brought about in man by a first infection is, as a rule, not manifested by a complete resistance to exogenous reinfection but by the much greater tendency in infected beings to a stricter localization of the lesion and by a greater tendency toward productive and fibrotic lesions. The first focalization of bacilli occurs as a rule in the parenchyma of the subpleural layers of the lung, relatively rarely in the apex. The earliest lesion is a tuberculous pneumonia, which soon becomes surrounded by proliferative tissue changes from which a dense fibrotic capsule develops around the center, which in turn undergoes caseation and calcification. Simultaneously or somewhat later the mediastinal lymph nodes become involved through lymphatic transport of bacilli; they undergo rapid caseation and then show more or less completely the same retrogressive changes as does the parenchymal lesion. The most frequent development of this primary complex, consisting of a parenchymal and lymphoglandular focus, is retrogression without clinical disease, leaving the unmistakable pathologic marks of a well demarcated parenchymal calcified focus and, frequently multiple, calcifications in the mediastinal lymph nodes. In this stage the tuberculous infection may remain and does remain in the majority of all infected persons; a scar, as it were, with which allergy caused by the infection is then the only mark left. In some cases the parenchymal focus may progress by contiguous spread, causing extensive caseous pneumonias and excavations. More frequently the parenchymal focus heals, while the lymphoglandular focus smolders on for greatly varying periods, at intervals discharging bacilli into the lymph and blood stream. The bacilli may focalize anywhere in the body, causing bone lesions, urogenital disease, scattered lobular pneumonic foci (usually in the upper portions of the lungs); or, if a massive discharge of bacilli from a liquefied caseous lymph node occurs, the result may be a generalized miliary tuberculosis.

The so-called secondary stage may never occur; or, again, it may manifest itself at any later stage of the disease. Pulmonary lesions similar to those seen during childhood in the phase of early dissemination are sometimes seen in adults. It is likely that the majority result from lymphohematogenous spread from primary lymph node foci. The pulmonary foci—true hematogenous tuberculosis—are symmetrically seeded throughout both lungs. Not infrequently they heal clinically by resorption, fibrosis, or calcification; others excavate and then continue the usual course of bronchogenic phthisis. Following the more or less complete healing of the primary complex or subsequent to major or lesser manifestations of early dissemination, a latent period usually intervenes before tuberculosis in the adult develops. In many cases of early dissemination, no further clinical manifestations occur.

The typical pulmonary tuberculosis of adult life begins in most cases with a single, initially exudative, focus. There are essentially three mechanisms by which this clinically primary focus may develop: (1) A bronchogenic spread occurs from incompletely healed apical lesions, the remnants of foci produced by early dissemination. (2) Bacilli from a still active primary lymph node focus are discharged into the lymph stream, are carried into the blood stream, and are filtered out in the lung. (3) Bacilli are inhaled from the outside. Regardless of the mechanism by which the new focalization takes place, the early lesion is a tuberculous lobular pneumonia, which is seen most frequently in the subapical region. This lesion is always unstable; it soon progresses or retrogresses. Demonstrable involvement of the regional lymph nodes practically never occurs. This exudative focus, the so-called Assman focus, or early infiltrate or infraclavicular infiltrate, again is subject to all the potential developments: resorption, fibrosis, caseation, liquefaction, excavation. If a cavity develops, a frank and perilous source of bacillary dissemination is established, from which at any time new bronchogenic spread may occur. From this point on, bacillary propagation through preformed channels, and localized destructive lesions constitute the main character of the disease. Within the lung this means bronchogenic spread, and beyond its boundary it means ulcerative tuberculosis of the larynx and the intestine.

CHARLES G. SUTHERLAND, M.B. (Tor.).

Tuberculosis of the Clavicle: Review of the Literature and Report of a Case. Jacob Sirkin and E. A. Baumgartner. Jour. Am. Med. Assn., July 11, 1936, **107,** 120–123.

The authors were able to find record of 30 cases in the literature. Most of the patients were between 10 and 40 years of age, only four of them being over 50 years of age. The disease is about equally frequent in the two sexes. There was no apparent predilection for either clavicle. There appears to be no anatomic or pathologic reason why primary involvement of the clavicle cannot occur. Other co-existing foci of tuberculosis were described in eleven cases, bone involvement in four; in the others the lungs, glands

of the neck, kidney, and breast showed tuberculous lesions. The patient whose case they report had a tuberculous kidney successfully removed some time before and x-ray examination showed a lesion of the sacro-iliac joint with the characteristics of a tuberculosis.

CHARLES G. SUTHERLAND, M.B. (Tor.).

TULAREMIC PNEUMONIA

Tularemic Pneumonia. LeRoy H. Sloan, A. S. Freedberg, and J. C. Ehrlich. Jour. Am. Med. Assn., July 11, 1936, **107,** 117–119.

Tularemia is a relatively newly described disease in the medical literature. In 1924 Verbrycke first made mention of a pneumonic process specific for this disease in the report of a fatal case, with the necropsy findings. The first mention of tularemic pneumonia as a clinical entity appeared in 1931, when three separate cases were reported in the literature. Only one instance of recovery of the organism from the sputum was recorded. The frequent association of caseous pneumonia with tularemia makes it reasonable to assume that an atypical pneumonia developing in a patient with a clinical history of tularemia, particularly if associated with pleural effusion, the pneumonia running a protracted course and the failure to establish tuberculosis or other specific granulomas as the causative factor, ought to be sufficient evidence to establish the clinical diagnosis of tularemic pneumonia. The physical and x-ray signs of pulmonary consolidation appear quite late in the course of the disease and do not disappear until long after apparent clinical recovery, if at all. The process evidently begins with involvement of the hilus, which then spreads peripherally. The authors report a case in which recovery was complicated by a spontaneous pneumothorax.

CHARLES G. SUTHERLAND, M.B. (Tor.).

TUMORS (DIAGNOSIS)

Neuroblastoma, from the Standpoint of the Roentgenologist. E. L. Rypins. Ill. Med. Jour., November, 1936, **70,** 431–436.

Rypins reports three children, aged 4, 4, and 5 years, with proptosis, hydrocephalus, marked secondary anemia with destructive and proliferative lesions involving the greater portion of the skeletal system, including both the long and the flat bones. No abdominal tumors were palpable. X-ray examinations showed the presence of a peculiar type of periosteal reaction, or "whiskers," along the left ischium in one patient, and along the lower end of both femora in another. When occurring in the skull, this periosteal reaction is said to give a "porcupine" appearance. These changes, in conjunction with the widespread destructive process, Rypins considers sufficient for a definite diagnosis of neuroblastoma. Pathologic diagnosis may be difficult, especially in the absence of cell arrangements known as "rosettes." The tumors are sensitive to irradiation if treated while the patient is still in a relatively good condition. All three cases reported by the author, however, died.

W. A. SODEMAN, M.D.

TUMORS (THERAPY)

Radiotherapy for Primary Malignant Tumors of Bone. Ettore De Bernardi. Archivio di Radiologia, 1936, **12,** 42–48.

The author reports four cases of bone tumor, three of which were treated with x-rays with satisfactory results. He feels that radiotherapy is the method of choice in the treatment of these tumors.

E. T. LEDDY, M.D.

Roentgen Therapeutic Results in Bone Tumors. G. Schulte. Strahlentherapie, 1936, **57,** 370.

The author reports a number of cases with bone tumors in which protracted fractional roentgen therapy has been of benefit. As a therapeutic test it was also helpful. The cases reported include a multiple osteohemangioma, osteo-epulis of the mandible, chondroma of the shoulder and hip, multiple myeloma, and Ewing's sarcoma.

ERNST A. POHLE, M.D., Ph.D.

Malignant Bone Tumors Cured by Radiation Therapy. A. U. Desjardins. Strahlentherapie, 1936, **56,** 583.

The author describes the use of his technic of "convergent" fields in the treatment of malignant bone tumors. Fairly high doses can be delivered to the neoplasm in this manner without danger to the skin. Three illustrative case reports are appended.

ERNST A. POHLE, M.D., Ph.D.

UNCLASSIFIED[1]

The New Institute of Radiology and Biophysics in Istanbul. Friedrich Dessauer. Strahlentherapie, 1936, **56,** 389–395.

This is a brief description of the radiological institute which the author is developing at the University of Istanbul in Turkey. It offers complete facilities for teaching and research; there are also wards in which to hospitalize patients with malignant disease while under treatment.

ERNST A. POHLE, M.D., Ph.D.

Physics and Radiology. J. A. Crowther. British Jour. Radiol., December, 1936, **9,** 767–775.

In an expression of appreciation of the honor conferred upon him by his election, the President of the British Institute of Radiology traced the relationship

[1] The abstracts under this heading are of undoubted interest, yet they do not fall under any single grouping. It has been thought best to let our readers have access to them under this heading.

of physics to radiology. Physics and medicine have been more closely associated in the past than is generally realized, for every physical discovery of any importance has been followed by an attempt to apply it therapeutically. The discoveries of magnetism, electromagnetic induction, and of radium and the x-rays are well-known examples.

The contributions of medical men to the science of physics should not be forgotten. We owe the discovery of magnetism and the name of "electricity" to the Colchester physician, Sir William Gilbert. Galvani was a Professor of Obstetrics and not of Physics. Dr. Thomas Young contributed valuable fundamental information of the wave theory of light, and of other subjects of physics in his studies, which were pursued with the object of making them subservient to the practice of medicine. Until recent times the contributions of physicists to the art of medicine were not so notable, although Robert Boyle was responsible for the employment of plaster of Paris and of gelatine for anatomical injections.

The first great contribution of physics to medical science were the discoveries of x-rays and radio-activity, by Thomson, Röntgen, Becquerel, and Curie in 1895 and 1896. X-rays differ in many respects from a new drug or serum. While the dosage of the drug can be dispensed by counting tablets, or by weighing, and the dosage of vaccine or serum can be determined in the physiological laboratory, the x-rays must be measured at the time they are produced.

Many problems regarding the dosage of x-rays have yet to be solved. The association of soft rays, medium rays, and hard rays in the same beam; the production of rays which may vary from 60 kv.p. or less to 600 kv.p. or more; the relationship of rays of relatively long wave length expressed in roentgens with a similar dose in roentgens of rays of short wave length; the action of x-rays on the individual cell or on the colloids of the organism are examples of the problems which emphasize the importance of the close co-operation of physics, physiology, and chemistry. The progress in refinement of apparatus has been considerable, and the gap between modern x-ray equipment and primitive outfits is greater than the "jagged flint used by the prehistoric surgeon in his operations and the modern surgeon's scalpel." The advance through constant improvement from the old gas tube, and the adoption of a scientific unit for measuring the output of radiation have been significant in modern therapeutic roentgenology.

In radiography much is expected from cine-radiography in the future. Dr. Russell Reynolds, while not a physicist, should be congratulated on excellent experimental research in the development of this method.

Dr. Strangeways' well-known original experiment on the irradiation of tissue cells has been extended and amplified by Dr. Mayneord "in a brilliant piece of mathematical deduction."

While the strict division of the total of human knowledge into numerous, distinctly separate sciences has served many useful purposes in the past, "the partitions are growing thin. . . . There are many problems, and that of the action of radiation on the cell seems to be one of them, where a joint attack promises the best hope of success."

That radiology is a science of many ramifications is fully appreciated by all, and the necessity for the organization of the British Association of Radiologists, as recently set forth by the President of that new organization, is recognized. With the necessary good will, the close co-operation of the British Institute of Radiology and the new British Association of Radiologists should do much for the advancement of physics and radiology.

J. N. Ané, M.D.

The New Roentgen and Radium Institute in Aarhus, Denmark. Carl Krebs. Strahlentherapie, 1936, **56,** 456–465.

The new Roentgen and Radium Institute erected recently in Aarhus, Denmark, is described by the author. Photographs of the building, floor plans, and a description of the apparatus used are appended.

Ernst A. Pohle, M.D., Ph.D.

Wilson Photographs of Roentgen Rays Passing through Matter. L. Grebe. Strahlentherapie, 1936, **56,** 603.

The author demonstrates six Wilson photographs taken in the "cloud chamber," showing the path of electrons after passage of the x-ray beam through air, air-equivalent material, and gold. The long path of the photo-electrons as well as the short path of the recoil electrons are shown in the illustrations.

Ernst A. Pohle, M.D., Ph.D.

The Morphologic Relationships between the Heart and the Stomach in Proportion to the Constitution of Fifty Soldiers as Shown by Radiologic Studies. Luigi Semmola. Archivio di Radiologia, 1935, **11,** 379–396.

The soldiers in this study were grouped according to Viola's classification and were studied by orthodiagram. Semmola's findings in regard to the size and shape of the heart and stomach agree with those of other authors, and he points out the various similarities and differences he found with respect to the body type of the individual.

E. T. Leddy, M.D.

Concerning Bridges between the Clinoid Processes: Technical Demonstration of Clinoid Processes and of Clinoid Bridges. Ludwig Haas. Fortschr. a. d. Geb. d. Röntgenstrahlen, February, 1935, **51,** 147–152.

This is in reality two short papers, one stating that osseous bridges between the anterior, middle, and posterior clinoid processes are normal variations and have, for instance, no relationship to bronchial asthma, as maintained by Bien; the second illustrating beautifully that detailed views of the clinoid processes of the

side close to the film may be obtained by limited tube shifting in either the vertical or caudal direction, from the point of typical centering and aiming at the sella itself instead of its point of projection to the temporal surface—at an angle of about 15 degrees in either vertical or caudal direction.

H. A. JARRE, M.D.

THE UTERUS

External Irradiation with Roentgen Rays of 200 and 300 Kv. as Initial Treatment in Carcinoma of the Cervix. M. R. Mathey-Cornat. Strahlentherapie, 1936, **57,** 313.

The author believes that in the treatment of carcinoma of the cervix it is preferable to use roentgen rays externally first, before applying radium intra-uterine. Technic: 200 kv., 2 mm. Cu + 2 mm. Al, 5–10 r per minute, 40–60 cm. F.S.D., 4–6 fields of 15 × 15 or 15 × 20 sq. cm., 3,000 r per area and 3,000 to 3,500 r effective in the vagina. When 300 kv. are used the depth dose is still better, at the same time sparing the skin from excessive doses. In the more advanced cases this preliminary roentgen therapy often renders the cervical canal patent.

In the author's experience this desirable effect was obtained in from 48 to 49 per cent of the early and borderline cases and in from 40 to 41 per cent of the advanced cases. He also has the impression that intra-uterine radium treatment is tolerated better if x-ray therapy has preceded it. Hospitalization of the patient during this combined x-ray and radium treatment is necessary.

ERNST A. POHLE, M.D., Ph.D.

Are the Operative Results in Carcinoma of the Cervix Improved by Post-operative Irradiation? H. R. Schinz. Strahlentherapie, 1936, **57,** 393.

The author studied the statistics published in the world literature regarding the percentage of cures in patients with carcinoma of the cervix treated by operation alone or by operation plus irradiation. After a critical analysis of the available figures and the calculation of the mean error, he comes to the conclusion that the combined treatment is at least 7 per cent (theoretical calculation) or 3.3 per cent (empirical calculation) superior to operation alone.

ERNST A. POHLE, M.D., Ph.D.

XANTHOMATOSIS

Xanthomatosis (Schüller-Christian's Disease). Robert A. Strong. Jour. Am. Med. Assn., Aug. 8, 1936, **107,** 422–425.

This term is used to describe a syndrome of certain bony defects in the skull, diabetes insipidus and exophthalmos. Hand presented the first case in 1893, believing it due to tuberculosis. Schüller reported two cases in 1915 and felt that the skeletal defects were secondary to disease of the hypophysis cerebri. Christian reported a case in 1919 and considered that the syndrome was due to a pituitary disturbance. It has since been established that the bony defects are predominantly the initial symptom. Rowland (1928) reviewed the literature extensively, presented two cases of his own, and was the first to prove that Schüller-Christian's disease belonged in the same class with all the other diseases due to defective lipoid metabolism. He suggested the name "xanthomatosis."

Five clinical entities have been included under the general heading of xanthomatosis by several writers. They are Gaucher's disease, Niemann-Pick's disease, Schüller-Christian's disease, the xanthomas occurring in icterus, diabetes, and pregnancy, and the so-called essential xanthomatosis.

The etiology is unknown, the etiologic factor common to all apparently being a disturbance of lipoid metabolism or of lipoid excretion, resulting in the storage of various forms of lipoid material in the organs or tissues of the patient. They may be either widespread and diffuse (as in Niemann-Pick's and Gaucher's disease), or localized in granulomatous deposits, as in Schüller-Christian's syndrome and the cutaneous xanthomas. The xanthoma cell is a cell of reticulo-endothelial origin infiltrated with lipoids, and the reticulo-endothelial system is said either to remove an excess of lipoids from the tissues or to store an excess in areas in which trauma or infections may have stimulated a collection of histiocytes.

The most hopeful treatment for this condition is through diet and roentgen therapy applied to the areas of lipoid deposit. This apparently benefits the bone defects but does not improve the exophthalmos.

In the discussion, Wahl pointed out that in Gaucher's disease the lipoid is a kerasin; in Niemann-Pick's disease it is a lecithin, while in Schüller-Christian's disease it is a cholesterin compound.

CHARLES G. SUTHERLAND, M.B. (Tor.).